COMPARATIVE STUDY OF TREATMENT OF CHILDHOOD VITILIGO 0.03% TACROLIMUS VERSUS 0.03%TACROLIMUS AND TOPICAL STEROIDS.

Dissertation Submitted to
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
in partial fulfillment of the regulations
for the award of the degree of

M.D. (Dermatology, Venereology and Leprology)
BRANCH – XX

CHENGALPATTU MEDICAL COLLEGE
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI, INDIA.

APRIL 2013

CERTIFICATE

Certified that this dissertation entitled **"COMPARATIVE STUDY OF TREATMENT OF CHILDHOOD VITILIGO 0.03% TACROLIMUS VERSUS 0.03% TACROLIMUS AND TOPICAL STEROIDS"** is a bonafide work done by **Dr. RASHMI SRIRAM**, post graduate student of the Department of Dermatovenereoleprology, Chengalpattu Medical College, Chengalpattu, during the academic year 2010 – 2013. This work has not previously formed the basis for the award of any degree.

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DECLARATION

I, **Dr. RASHMI SRIRAM,** solemnly declare that dissertation titled, "**COMPARATIVE STUDY OF TREATMENT OF CHILDHOOD VITILIGO 0.03% TACROLIMUS VERSUS 0.03%TACROLIMUS AND TOPICAL STEROIDS"** is a bonafide work done by me at Chengalpattu Medical College during 2010-2013 under the guidance and supervision of **Prof. Dr Hameedullah MD DD .,** Professor and Head, Department of Dermatology, Chengalpattu Medical College, Chengalpattu.

The dissertation is submitted to The Tamilnadu, Dr. M.G.R. Medical University, towards partial fulfilment of requirement for the award of **M.D. Degree in Dermatology, Venereology and Leprology**

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Place : Chengalpattu. **(Dr RASHMI SRIRAM)**

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INTRODUCTION

Vitiligo was referred by various names such as ‘Sufaid Dagh’, ‘Phulbahari’, ‘Bars’, ‘Bahak’, ‘Kilas’, ‘Palita’, ‘Kodha’, ‘Sweta Kushta’, ‘Dhawal Kustha’.[1] However origin of the term ‘Vitiligo’ is obscure.

Vitiligo is a common skin disorder affecting between 1-2% of world population.[1] In India and different countries across the globe the incidence ranges from 0.1 - 8.8%.The highest incidence has been reported in India followed by Mexico and Japan. [1] It affects 50% of patients before 20 years of age and 25% before 10 years of age, resulting in a significant pediatric problem.

It is characterised by completely depigmented milky white macules of varying sizes. This disorder does not cause restriction in capacity to work or expectancy of life. It leads to cosmetic disfigurement causing considerable psychological trauma to patients.[2]

Various theories such as autoimmune, autocytotoxic , aberration of cellular immunity with melanocyte destruction, inhibition of melanogenesis and aberration of vitamin D3 metabolism are proposed as possible causes.[3]

There are various medical and surgical modalities available for the treatment of vitiligo, but all of these cannot be used in children. Medical therapy is considered the first line of management in this age group.[4]

60% of pediatric patients respond atleast particularly to application of medium strength to potent topical steroids alone. [4]

Tacrolimus is a macrolide immunosuppressant that is approved for use in adult patients and pediatric patients above the age of 2 years. It acts by inhibiting the activation and maturation of T cells by means of blocking the action of calcineurin and interleukin (IL)2, IL-4and IL-5 transcription. In vitro studies have demonstrated the positive effects of this drug in vitiligo by showing an increased proliferation of melanocytes and melanoblasts in epidermal cell cultures. The repigmenting effect of tacrolimus has been reported to be site dependent and best results are seen on face and neck.[5]

Therefore the present study was done to compare the efficacy of 0.03% tacrolimus alone and 0.03% tacrolimus and mid potent topical steroids. In fact the site dependent effect of tacrolimus gives an indirect support to the idea of combined role of topical tacrolimus and topical steroids.

REVIEW OF LITERATURE

Vitiligo is a common, acquired, primary, progressive, melanocytopenia of unknown etiology, manifesting clinically as circumscribed achromic macules often associated with leucotrichia and histologically by degeneration and disappearance of melanocytes in the involved skin and not infrequently in pigment epithelium of the eyes, leptomeninges and inner ear.[6,7]

Historical aspects

The earliest authentic reference of the condition can be traced back to the period of aushooryan (2200BC), in the classic tarikh – e - tib – e - iran. Pharonic medicine in ebers papyrus (1550BC) described two types of diseases affecting the colour of the skin, with tumours, probably leprosy and with only colour change, probably vitiligo.[8]

The origin of the term vitiligo is obscure, like the disease itself. Some believe that it is derived from the latin word ‘vitelius’ meaning vale i. e., pale pink flesh of calf, since the clinical lesions resembled the white patches of spotted calf, while other believed that it originated from latin word ‘vitium’ meaning blemish. The roman physician celsus first used the term vitiligo in second century A D. It is interesting to note that the Rig-

Veda (6000 BC or earlier) named leukoderma as kilas meaning white spotted deer. [9]

The Indian sacred book Atharva Veda dating back to 1400 BC refers to disease as kilas meaning white in Sanskrit. In charaka samhitha dated back to 800 BC refers to disease as svitra. In the Sanskrit dictionary Amarkosha (600AD), the word is translated as spreading whiteness. In vinayak pitak (624 – 544BC) the sacred book of Buddhism there is mention of disease associated with white spots.[10]

The Manu smruti dating back to 200 BC mentions the word Sweta Kustha which means that which make the body ugly or spoils the blood.[11]

In Amarkosha the term svitra has been used synonymously with padosphota meaning flower of legs, twakpuspi meaning flower of skin and sidhmati which means spreading whiteness.[12]

Moritz Kaposi was one of the first to describe the histopathological features of vitiligo. [11]

EPIDEMIOLOGY

The prevalence of vitiligo in childhood (age < 12 years) has been quoted to be around one quarter of vitiligo patients of all ages.[13] Both sexes are equally affected. The female prevalence is higher due to greater concern about the cosmetic defect.[1]

Vitiligo appears to be observed more commonly in sun-exposed areas and in darker skin types. [1] It affects people with skin types 3 and 4. Diet which is poor in protein and cuprominerals is thought to be contributory to vitiligo.[14]

Vitiligo may develop at any age. Onset of the disease is usually below 10 years of age. The mean age of onset of childhood vitiligo in an Indian study was 6.2 years.[14] Family members of the affected children have higher incidence of vitiligo and other autoimmune diseases.[15]

AETIOPATHOGENESIS

The pathogenesis of vitiligo is complex and not well understood. Over the years multiple aspects of biochemical, immunological, genetic aspects play a role and so far no convincing model describing the interplay of all contributing factors have been formulated.[16,17]

GENETIC FACTORS AND INHERITANCE

At present the consensus is that familial incidence is between 20 -30%.[18] Inheritance was thought to be autosomal dominant with variable expression and incomplete penetrance.[19-21] The possibility of autosomal recessive or polygenic inheritance with its somatic expression decided by precipitating factors has been suggested. Monozygotic twins have been seen to have vitiligo with a similar or dissimilar mode of onset, type, extent and course of the disease.[22]Various susceptibility loci for vitiligo are AIS1(chr1), AIS2(chr 7),AIS3(chr8) and SLEV1(chr 17). Association of vitiligo with transporter associated with antigen processing protein- 1(TAP-1) gene is suggestive of possible role of MHC class I antigen in antimelanocyte autoimmune response.[23] An association between the catalase gene (CAT) and vitiligo has been suggested.[24] VIT- 1 gene which maps to chromosome 2p16 has also been associated with vitiligo. Recently variants of gene NALP1 on chr17p13 were found to be associated with group of epidemiologically associated autoimmune and autoinflammatory disease including generalised vitiligo and autoimmune thyroid disease.[25]

No definite human leukocyte antigen (HLA) association is established for vitiligo although increased incidence of HLA DR4 in black people, HLA B13 in Morocean Jews and HLA BW35 in Yemenite Jews with vitiligo have been reported.[25]A familial incidence of diabetes mellitus and thyroid

disease has been noted in cases of vitiligo.[26] Atopy is another familial association.[18]Various triggering factors include emotional stress, drug intake, infections, trauma/injury[1]

THEORIES ON THE PATHOGENESIS:

Besides genetic predilection, diverse epigenetic factors also play a role in etiopathogenesis. An alteration in the microenvironment of epidermal melanin units , related possibly to immunological, neurochemical factors has been presumed. The following hypothesis have been proposed.[27]

1. NEURAL HYPOTHESIS[16,17]

Evidence in favour are

1. The peripheral nerve endings may secrete a substance that is cytotoxic to melanocytes and causes their destruction. This is supported by segmental variety of vitiligo which occurs in specific dermatomes.
2. Associated with encephalitis and trauma that causes peripheral nerve damage.
3. Production of abnormal neuropeptides and nerve growth factors which are toxic to melanocytes.

4. Abnormal autonomic function such as increased adrenergic tone, increased norepinephrine and an increased concentration of catecholamines.
5. The common embryologic origin of melanocytes and the nervous system.
6. Demonstration of direct contact between cutaneous free nerve endings and epidermal melanocytes in vitiligo macules.
7. Repigmentation in segmental lesion was observed by administration of nialamide, an oral MAO inhibitor to suppress metabolism of catecholamines at sympathetic nerve endings.[18]

2. **SELF DESTRUCTIVE THEORY BY A.B.LERNER.**

This hypothesis envisages that an intermediate metabolite of melanin synthesis cause destruction of melanocytes or that the normal process of melanosome degradation proceeds unabated to cause melanocyte death.

Elimination of toxic melanin precursors does not possibly occur, eventually causing death of melanocytes. Supportive evidence includes :

1. The appearance of vitiligo in areas which are usually darkly pigmented.

2. Phenolic compounds have the potential to produce vitiligenous lesions.
3. Tyrosine, dopa and tryptophan have a selective toxicity towards melanocyte.

   A phenolic derivative may emerge as a degradation product of melanogenesis can cause tyrosinase inhibition.[27]

   The enzyme thioredoxin reductase, a free radical scavenger is located on the membrane of melanocytes. This enzyme is inhibited by calcium. Higher extracellular calcium levels cause increased superoxide radicals that lead to inhibition of tyrosinase by upsetting the equilibrium of oxidised and reduced thioredoxin in the epidermis, which later causes cell death. [28]

3. **AUTOIMMUNE THEORY**

An aberration of immune surveillance has been surmised as the basic event responsible for dysfunction and destruction of melanocytes. Primarily there may be some kind of biochemical trauma to melanocytes resulting in release of antigenic substances and subsequent autoimmunisation. Alternatively there may be immune cells directed against the component of autologous melanocytes. The frequent association of vitiligo with

autoimmune disorder and frequent presence of autoantibodies against thyroid, thyroglobulin, adrenal, parietal cells, malignant melanoma and halo nevus. 20-30% of patients with vitiligo can have an autoimmune endocrine disorder. There have been reports of IgG antibodies to melanocytes, nevus cells and melanoma cells. Complement fixing antibodies against vitiligo is seen in mucocutaneous candidiasis, alopecia universalis or multiple endocrinopathies.

Cell mediated immune defects such as decreased responses to dinitrochlorobenzene; quantitative T cell defects, defective natural killer cell activity and decreased lymphoproliferative responses to multiple mitogens. There is significant decrease in CD45A+ and significant increase of HLA-DR+ cells indicating the presence of activated peripheral T cell dysregulation. Hence both humoral and cell mediated immune defects are involved.

4. CONVERGENCE THEORY.

Convergence theory states that genetic factors have a role in causation of vitiligo in addition to other elements such as stress, accumulation of toxic compounds, infection, autoimmunity, mutations, altered cellular environment, and impaired melanocyte migration and proliferation.[5]

5. MELANOCYTE GROWTH FACTOR REDUCTION HYPOTHESIS.[29]

According to this theory there is a growth factor produced by keratinocytes, fibroblasts, various other tissues which regulate the normal density of melanocytes and the deficiency of the growth factor leads to depigmentation in vitiligo.

6. ANTIOXIDANT DEFICIENT THEORY.

There is breakdown in the antioxidant defence in the epidermis leading to melanocyte toxicity. An abnormally high level of catecholamine discharge in epidermis and dermis could lead to ischemia and subsequent overproduction of reactive oxygen species. This oxidative stress leads to accumulation of high level of 6,7 biopterins which inhibits tyrosinase activity and extremely cytotoxic to melanocytes.[30]

7. A NEW INTEGRATED THEORY.

It takes into account melanocyte detachment and transepidermal elimination, neural- biochemical, and autoimmune hypothesis. It proposes that non segmental vitiligo is a primary melanocytorrhagic disorder and altered melanocyte responses to friction and possibly other types of stress, inducing their indolent detachment and subsequent transepidermal loss.

Adhesion system of melanocytes is far weaker and loss of dendricity could also affect the melanosome transfer and contribute to depigmentation. Damaged melanocytes may release melanosomal antigens which could induce an immune response.[31]

8. APOPTOSIS IN VITILIGO MELANOCYTES.

It can be induced by variety of cytokines, some environmental chemicals or other molecular mechanisms. The outcome of the signal depends on the balance between pro- apoptotic and anti-apoptotic factors. Caspase -3 is the key mediator of apoptosis and accelerates a cascade of caspases leading to degradation of the cell.[31]

CLINICAL FEATURES

A typical lesion is a well defined depigmented macule, which often shows variable number of depigmented hair and without any change in skin texture. Onset of the lesions is usually insidious. The disease is progressive in nature as a rule and course is virtually unpredictable The initial lesion may be macules varying widely in size, shape, number and location. Frequently, the initial macule occurs on the exposed areas (such as the dorsal surface of hands, elbows, feets, legs, knees, neck and face), body

folds (such as axillae, groin, and sub mammary region in women), lips or genitalia.[6,32]

The initial unifocal lesion may be followed by the appearance of new lesions elsewhere.

In less than 25% of cases the onset may be multifocal. [6] Involvement of pretibial region, palms and sole are quite common in India. [18]

Achromotrichia is a common feature of vitiligo lesions on hairy parts. White hair is of some diagnostic and prognostic significance, the former because they help in differentiation from other hypopigmented macules and latter because they indicate poor repigmenting capacity. [33]

Vitiligo vulgaris is the most common clinical type in childhood vitiligo, followed by focal vitiligo and segmental vitiligo. Mucosal vitiligo is rarer in children compared to adults. The rarest type seen in childhood vitiligo is the universal vitiligo. [34]

Common initial site of onset of both non segmental vitiligo and segmental vitiligo in children is the face and neck. In nonsegmental vitiligo, initial lesions are periocular, perinasal or perioral and gradually spread to other body parts. Perineum, perianal area and in infancy, the diaper area may be the initial site of occurrence of lesions. Majority of the children have less than 20% body surface involvement.

Scalp leukotrichia is a frequent finding in children with vitiligo and their family members.

Koebner's phenomenon can be noted in both segmental and nonsegmental vitiligo in children, more commonly in the latter type. Koebner's phenomenon is more common in childhood vitiligo because of higher mobility and playfulness in this age group. Presence of Koebnerisation is indicative of disease activity. [34]

Emotional trauma and repression have been noted to be responsible for very sudden onset, rapid extension and spread of lesion. Such cases are referred to as 'valeceo' type vitiligo.

A positive family history, fewer lesions, less than 5% of body surface area involvement, frequent segmental involvement, and greater difficulty in treatment but relatively better prognosis are the hallmarks of childhood vitiligo. [35]

Morphological variations on the typical vitiligo macule [36]

1. Trichrome vitiligo refers to the presence of intermediate colour; this is a uniform tan coloration that is narrow to broad interface between the normally pigmented skin and central depigmented macule.

2. Quadrichrome refers to the fourth colour; this is macular perifollicular or marginal hyperpigmentation seen in some cases of repigmenting vitiligo.
3. Pentachrome vitiligo also may be observed. This includes a depigmented macule, tan, brown hyperpigmentation, blue-gray hyperpigmentation and normal pigmentation.
4. Blue vitiligo corresponds to vitiligo macules occurring in sites of post inflammatory hyperpigmentation.
5. Inflammatory vitiligo has an erythematous, raised border.
6. Confetti macules, which are typical in colour but only 1 to 2 mm in diameter, may occur randomly or may be perifollicular.

Classification

1. **Classification of vitiligo according to extent of involvement and the distribution of depigmentation.[37,38]**
    a. Focal vitiligo / vitiligo areata is an isolated macule or a few scattered macules: the macules are limited in both size and number.
    b. Segmental Vitiligo: Segmental vitiligo is characterized by unilateral macules and patches in a dermatomal or quasi-

dermatomal distribution. This tends to have an earlier onset, not associated with other autoimmune diseases. This type occurs commonly in children. Alteration in neural peptides is implicated as the pathogenesis. No koebnerisation present. More than 50% of the cases have patches of white hair known as poliosis.

c. Generalized vitiligo / Vitiligo vulgaris: This is the most common type of vitiligo are usually widely or symmetrically distributed.
d. Acrofacial vitiligo involves distal fingers and periorificial facial areas.
e. Lip – tip vitiligo- refers to a type where there is involvement of mucous membranes like lips, distal penis, nipples and distal parts of fingers and toes.
f. Vitiligo universalis / Universal vitiligo- In this type almost the entire body surface is achromic, with only few islets of normally coloured or hyperpigmented skin.
g. Combination Vitiligo: very rarely vitiligo vulgaris and segmental vitiligo are seen in the same patient.

2. Classification depending on prognosis of vitiligo.[1,5]

a. Progressive vitiligo (V1) – Vitiligo with developing new lesions, increasing old lesions and lesions with ill-defined borders.
b. Quiescent vitiligo (V2) – Vitiligo with no new lesions, stationary old lesions, decreasing lesions.

3. **Classification based on sweat stimulation studies.**[1,5]
    a. Type A is non dermatomal. It has potential for life long evolution, associated with koebner's phenomenon and frequently with autoimmune diseases.
    b. Type B is dermatomal. It has rapid onset and evolution. It has a stable course.

4. **Based on presence or absence of melanocytes.**
    a. Absolute
    b. Partial
5. **Based on etiopathogenesis.**
    a. Immune
    b. Neural
    c. Chemical

6. **Indian classification.**
    a. Segmental vitiligo (Vitiligo Zosteriformis).
    b. Non segmental (Focal vitiligo, acrofacial vitiligo, vitiligo vulgaris, mucosal vitiligo).

Assessing a person with vitiligo [39]

Determine the person's skin type (that is skin colour and ability to tan)

Determine whether the person has non segmental or segmental vitiligo.

Ask about previous episodes of spontaneous repigmentation, previous treatments and their effectiveness and any trauma preceding skin changes.

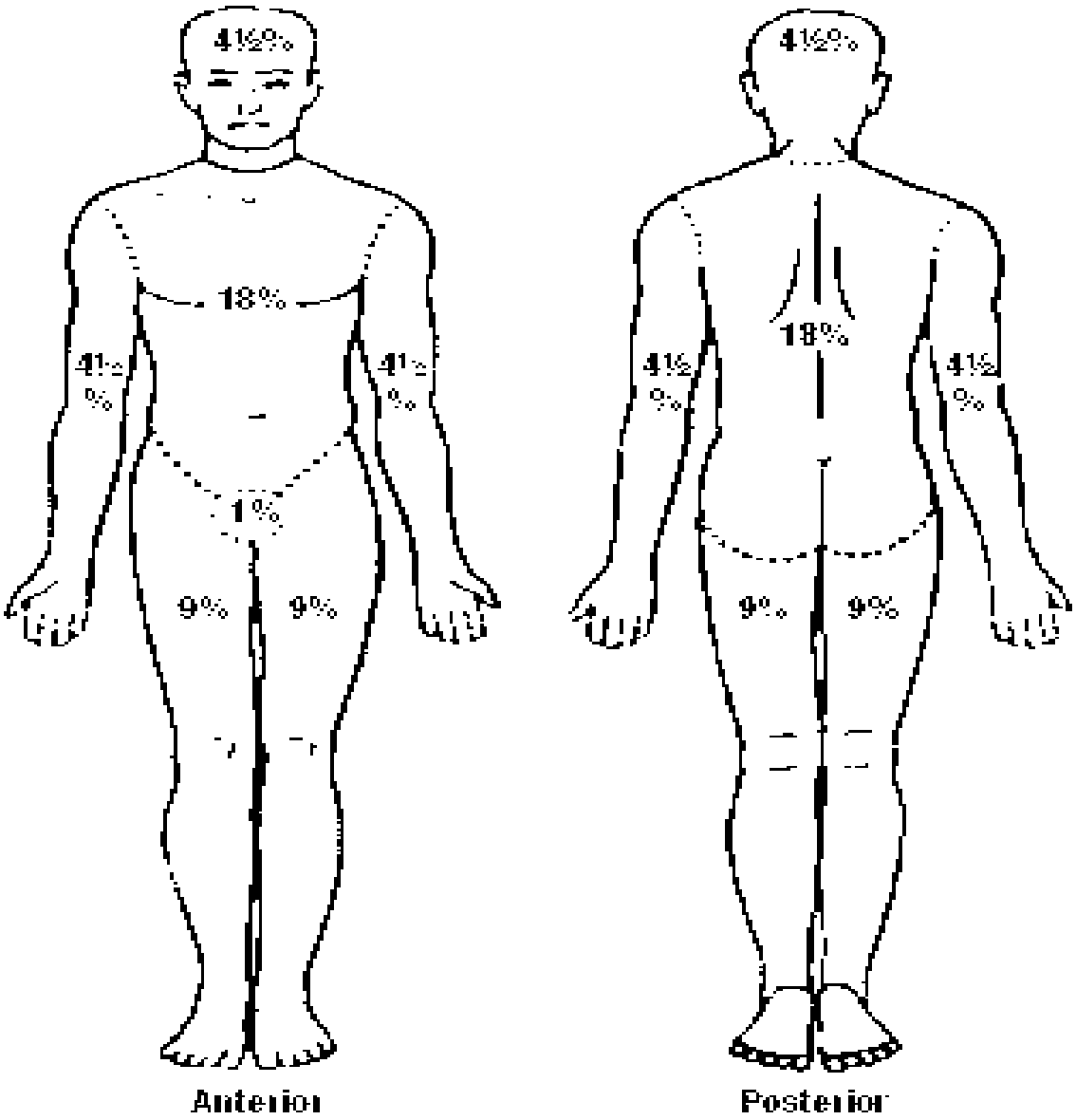
Assess the impact on quality of life.

For people with non segmental vitiligo

Note whether the face is affected.

Estimate the percentage of the body surface area that is affected using the Rule of Nine or the Lund and Browder chart.

The Rule of Nine



Lund and Browder chart

Adult		**Child**	
Anatomic Structure	**Surface Area**	**Anatomic Structure**	**Surface Area**
Anterior head	4.5%	Anterior head	9%
Posterior head	4.5%	Posterior head	9%
Anterior torso	18%	Anterior torso	18%
Posterior torso	18%	Posterior torso	18%
Anterior leg, each	9%	Anterior leg, each	6.75%
Posterior leg, each	9%	Posterior leg, each	6.75%
Anterior arm, each	4.5%	Anterior arm, each	4.5%
Posterior arm, each	4.5%	Posterior arm, each	4.5%
Genitalia/perineum	1%	Genitalia/perineum	1%
Adult, obese >80 kg		**Infant <10 kg**	
Anatomic structure	**Surface area**	**Anatomic structure**	**Surface area**
Head and neck	2%	Head and neck	20%
Anterior torso	25%	Anterior torso	16%
Posterior torso	25%	Posterior torso	16%
Leg, each	20%	Leg, each	16%
Arm, each	5%	Arm, each	8%
Genitalia/perineum	0%	Genitalia/perineum	1%

Ask about the duration of lesions and whether they are active and progressing, stable or regressing.

Vitiligo area scoring index. [40]

The percentage of vitiligo involvement is calculated in terms of hand units. One hand unit (which encompasses the palm plus the volar surface of all digits) is approximately equivalent to 1% of the total body surface area. The degree of pigmentation is estimated to the nearest of one of the following percentages:

100% - complete depigmentation, no pigment is present.

90% - specks of pigment present.

75% - depigmented area exceeds the pigmented area.

50% - pigmented and depigmented areas are equal.

25% - pigmented area exceeds depigmented area.

10% - only specks of depigmentation present.

The VASI for each body region is determined by the product of the area of vitiligo in hand units and the extent of depigmentation within each hand unit measured patch.

Total Body VASI = Σ [hand units X residual depigmentation] all body sites.

Classification of vitiligo associations

A. Skin disorders.

1. Alopecia areata in 5% of cases.[41]
2. Halo naevi.
3. Psoriasis.
4. Lichen planus.
5. Ichthyosis vulgaris.
6. Atopic dermatitis[42]
7. Bullous pemphigoid.
8. Dermatitis herpetiformis.[43]
9. Chronic actinic dermatitis.[44]
10. Twenty nail dystrophy.[45]
11. Connective tissue disorders: Morphoea, Lichen sclerosis, Lupus Erythematosus, DLE.[46.47]
12. Malignant melanoma.[48]

B. Ocular Abnormalities[49]

1. Iritis.
2. Careful examination revealed depigmentation in choroid and retina in up to 40% of cases.

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C. Auditory associations[50]

Sensory neural deafness.

D. Endocrine associations[42]

1. Thyroid abnormalities: either hypothyroidism or hyperthyroidism.
2. Diabetes mellitus: occurs in 1 to 7% of vitiligo patients and conversely, vitiligo occurs in 4.8% of diabetic patients.
3. Addison's disease in 2% of cases.
4. APECED: Increase in incidence (13%) of vitiligo in patients with autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy has been established. This is particularly seen in patients with extensive vitiligo.
5. Pernicious anaemia.
6. Hypoparathyroidism.
7. Myasthenia gravis and Thymoma.

E. Hematological associations[50]

1. Autoimmune hemolytic anaemia.
2. Lymphomas and Leukemias.
3. Pernicious anemia.

F. Infections[51]

1. Chronic hepatitis C
2. HIV Infection.

G. **Syndrome associated**[52,53]

1. Vogt Koyanagi Harada syndrome – It is a bilateral, diffuse granulomatous uveitis. It is associated with poliosis, vitiligo, alopecia, central nervous system and deafness.
2. Alezzandrini syndrome- This is an extremely rare syndrome characterised by unilateral impairment of vision, unilateral facial vitiligo and poliosis.

DIAGNOSIS [3]

1. Mostly clinical. Invasive and sophisticated investigations are not required.
2. Woods lamp examination – In children with fair skin as it is difficult to differentiate a lesion of vitiligo from surrounding normal skin. It can be clearly visible as amelanotic macules.
3. Complete blood count and fasting blood sugar as a routine workup in all patients.
4. Skin biopsy – in case of diagnostic difficulty.
5. Thyroid function tests.

6. Screening for auto antibodies – to rule out the associated autoimmune disorders (Antinuclear antibodies, Anti thyroglobulin antibody, Anti thyroid peroxidise antibodies).

HISTOPATHOLOGY:

The most prominent feature in vitiligo is alteration of melanocytes at dermoepidermal junction. With silver stains or the dopa reaction, well established lesions of vitiligo is totally devoid of melanocytes. The peripheries of the expanding lesions which are hypopigmented still show few DOPA positive melanocytes and some melanin granules at the basal layer. In outer border of patches of vitiligo melanocytes are often prominent and show long dendritic processes filled with melanin granules.

Histopathology of vitiligo in sections stained with H & E. [55]

It varies according to the type of the lesion that is biopsied as well as the biopsy site.

1. Early evolving lesion: Focal interface changes with vacuolization of basal cells with few lymphocytes in the basal cell layer in close proximity to melanocytes are seen in early lesions. Melanin is slightly reduced in the basal layer but with an almost normal

complement of melanocytes. These are inflammatory lesions, histologically showing sparse to moderate dense lympho-histiocytic infiltrate that is the adnexal structures and even around dermal nerve twigs.

2. Fully developed vitiligo of short duration: The epidermis is almost devoid of melanin but otherwise normal in thickness and structure. Melanocytes are usually absent. Such lesions often show the presence of several clear cells in the upper dermis, which have been shown to be langerhans cells. Sparse, superficial, perivascular inflammatory infiltrate with few melanophages.
3. Long standing lesions of vitiligo: There is complete absence of melanin from the epidermis and total absence of melanocytes. Various structural changes are present which point towards long duration. Epidermis is flattened with loss of normal rete ridge pattern and often shows hyperkeratosis. The papillary dermis shows moderate thickening with increased number of fibrocytes with thin elongated nuclei and thickened collagen.
4. Pigmented margins of vitiligo lesion: There is increased melanin in the basal layer, increased number of melanocytes often with large dendrites, and large melanocytes that contain abundant melanin in their cytoplasm.

5. Repigmenting vitiligo: Epidermis is flat and thin with absence of melanin and melanocytes. At places it shows normalization of its architecture with reappearance of the rete ridge pattern, presence of melanin in the basal cells with few melanocytes that show heavily melanized dendritic process.

Differential Diagnosis of childhood vitiligo. [56]

A. Congenital

1. Nevus Depigmentosus.
2. Nevus Anemicus.
3. Ash leaf spots(tuberous sclerosis)
4. Piebaldism.
5. Waardenburg syndrome.
6. Hypomelanosis of Ito.
7. Fourth stage of Incontinentia Pigmenti.
8. Oculocutaneous Albinism.
9. Vogt Koyanagi Harada syndrome.
10. Alezzandrini syndrome.

B. Acquired

1. Inflammatory – Pityriasis alba, Lichen Striatus, Post inflammatory hypopigmentation.

2. Infection – Pityriasis versicolor, Leprosy, Post Kala azar dermal leishmaniasis, Pinta.
3. Miscellaneous – Polymorphous Light eruption, Contact depigmentation, Lichen sclerosus et Atrophicus, topical steroid abuse.

COURSE OF CHILDHOOD VITILIGO

The course of childhood vitiligo is mostly stable or regressive; only few patients experience progressive or recurrent disease. Complete spontaneous repigmentation of non segmental vitiligo is unusual. However as compared to adults, the rate of spontaneous repigmentation is more in children, especially in tropical countries and in summer months. Repigmentation may be diffuse, marginal, perifollicular. Following onset segmental vitiligo spreads fast only along the affected dermatome. Thereafter it remains stationary for the rest of life. [34]

PROGNOSIS. [57]

There is no reliable indicator of good prognosis, but the following factors usually indicate a poor prognosis:

1. Lesions on the so called resistant sites, such as bony prominences, nonfleshy areas, non-hairy areas and mucosal areas. They comprise

the sides of ankles, front of wrists, back of elbows, dorsum of feet and hands, palms, soles, nipples and areola.

2. The greater the percentage of white hair the worse the prognosis.
3. Extensive long standing disease.
4. Associated ailments, especially systemic diseases.
5. Heridofamilial background.
6. Elderly age group.
7. Iatrogenic factors (injudicious administration of topical and systemic medications).

Treatment modalities of childhood vitiligo.

1. Medical.

a. Topical

   i. Corticosteroids.

   ii. Tacrolimus/Pimecrolimus.

   iii. Calcipotriol.

   iv. Pseudocatalase.

   v. Combination.

b. Systemic

   i. Corticosteroids (OMP with betamethasone/ methylprednisolone)

2. Phototherapy

i) Topical PUVA.

ii) NB-UVB.

iii) Systemic PUVA (>12 years).

iv) Phenylalanine + PUVA.

v) Excimer laser.

3. Surgical therapy

   i) Conventional – mini punch graft, Suction blister epidermal graft, Thin Thiersch graft.

   ii) Newer cellular transplantation techniques – Epidermal cell suspension, Cultured melanocyte suspension, Cultured epidermis.

4. Cosmetic camouflage.
5. Total depigmentation using Monobenzyl Ether of Hydroquinone [MBEH].

General Aspects. [59]

1. Patient should be explained the nature of the disease and its unpredictable course and prognosis.
2. Reassurance.
3. Balanced nutritious diet enriched with proteins, vitamin B complex, Vitamin E, and minerals such as copper, iron and zinc should be supplemented.

4. Avoidance of physical, chemical and emotional trauma as far as possible.
5. Avoidance of soaps, detergents and substances containing phenolic compounds, rubber goods and contact exposure to other chemical agents.
6. Avoidance of sunlight exposure, if necessary sunscreens are prescribed.

A. MEDICAL THERAPY

a. Topical

1. Topical steroids

Mid potent steroids are first line therapies for children with localised vitiligo. Although high potency steroids are more effective in vitiligo, these are not recommended for use in children. Available studies report a 45- 60% response rate to topical steroid in childhood vitiligo. According to Halder et al and Cho et al the response rate in children was 45% and 56% respectively with topical steroids alone.[61] It requires long term therapy for several months, increasing the chances of developing tachyphylaxis and local side effects like atrophy, telangectasia, hypertrichosis and striae. There are risks of serious side effects like glaucoma (prolonged application on periorbital vitiligo), suppression of hypothalamopituitary adrenal

axis and growth retardation with long term use over large body surface area. In order to avoid the side effects, interrupted therapy has to be given (application twice or once daily for 2 months followed by treatment free period for 2 weeks if the treatment period is longer than 8 months). Hence patients should be cautioned against inadvertent use of topical steroids. [34]

2. Topical Tacrolimus and Topical Pimecrolimus.

Topical calcineurin inhibitors (TCI), tacrolimus and pimecrolimus are effective alternatives to topical corticosteroids in terms of avoidance of side effects of the latter .TCIs are slower to exert beneficial effect compared to topical corticosteroid. Best response is observed on thinnest areas of the skin (eyelids).They are not approved for treatment of vitiligo in children below 2 years. Side effects are mild, transient and hence easily tolerated by children. However these agents are costly and may not be affordable by the families from low socioeconomic strata. [34]

3. Topical calcipotriol

It is a vitamin D analogue that could act in vitiligo by playing role in calcium regulation by 1, 25 dihydroxy vitamin D3 receptors on melanocytes and by regulation of calcium homeostasis. It has been reported to be an effective adjunctive treatment in vitiligo, enhancing

the efficacy of PUVA therapy.[57] Side effects are mild, transient and hence easily tolerated by children. However these agents are costly and may not be affordable by the families from low socioeconomic strata. [34]

4. Pseudocatalase.

Topical application of pseudocatalase and calcium chloride with short term suberythemogenic UVB used twice a day has been claimed to produce repigmentation in 90% of vitiligo patients. [58]

5. Basic Fibroblast growth Factor.

It is capable of multiplying melanocytes from surrounding hair follicles surrounding the affected skin and also acts a chemotactic agent to direct the new melanocytes to the vitiligo patch. [59]

6. Placental Extract Preparations.

The use of human placental extract both aqueous and alcoholic has been widely propagated. It probably rectifies the block in the conversion of tyrosine to dopa and dopa to dopachrome. The best results have been observed in focal and acral types of lesions but also effective in segmental and vulgaris types. The extract is to be applied locally three times a day. It should be rubbed in for 3 to 5 minutes followed by exposure to sunlight, infrared light and UV lamp for 15 minutes. [60]

b. Systemic

Corticosteroids

Rapidly progressive generalised vitiligo in older children and adolescents may be treated with a short course of systemic steroid. A better way to avert the side effects is administering oral betamethasone as a single morning dose (0.1 mg/kg body weight) on two consecutive days in a week (oral mini pulse therapy) for 12 weeks and thereafter reducing the dosage by 1mg/month for the next 3 months. [61]

c. **Nutritional agents.**

Multivitamin therapy, antioxidants, minerals given for a prolonged period has been useful in vitiligo patients. Oral Zinc is also said to be effective in vitiligo. [57]

B. PHOTOTHERAPY

The mechanism of action of psoralens and UVA therapy is by increase of the following:-

a. Number of functional melanocytes.
b. Number and size of melanosomes.
c. Number of dendrites of melanocytes.
d. Transfer of melanosomes to keratinocytes.
e. Tyrosinase activity.
f. Amount of free melanin.
g. Thickness, density and adherence of the stratum corneum.

1. **Topical PUVA**.

It can be used safely in younger children with limited body surface area [BSA] involvement. As a rule if the vitiligo macule is less than 6 sq cm in size, usually 0.1% can be applied weekly followed 2-3 hours later by solar UVA irradiation for 30-60 seconds. The time of exposure can be increased by 30 seconds per sitting and the frequency to twice weekly to thrice weekly sittings until the patch become slightly erythematous.

Alternatively, after 2-3 h of application, the area is exposed to black light at a distance of 4 cm for 4-5 min. After treatment the area should be washed and sunscreen should be applied. The treated area

should not be exposed to sunlight for atleast 12 hours to avoid phototoxicity. [57]

2. **NB- UVB**

Narrow band fluorescent bulbs of Philips TL-01, each of 100W with an emission spectrum of 311nm are used. No side effects of oral psoralen, can be used in pregnancy and childhood, no post exposure eye protection is required and exposure time is shorter are the advantages of this modality. The face and neck showed the best results, whereas the trunk and proximal extremities had moderate pigmentation. Acral areas and areas of bony prominences and lower hair growth density are hardly pigmented. If no response is seen after 6 months then further therapy should be discontinued. [62]

3. **Systemic PUVA**

The use of topical or oral psoralens and ultraviolet A radiation (UVA) termed PUVA. It is contraindicated in children less than 12 years of age.[63] These phototoxic compounds that enter cells and then absorb photons to produce photochemical reactions that alter the function cellular constituents. It is used when more than 20-25% of the BSA is involved or in patients where other modalities fail to give optimum results.[63] Three psoralens are used :- Methoxypsoralen or 8-MOP, Bergaptan or 5-MOP and Trioxsalen or

4,5,8 trimethyl psoralen.[64] Psoralens (8-MOP or TMP) are given in the dose of 0.6mg/kg/day ingested with food 2 hours before sun exposure, preferably between 11am and 1 pm..[65]

The first therapeutic dose is determined by calculating the minimal phototoxicity dose (MPD) which is determined by phototesting. If phototesting is not feasible then treatment is usually started at an initial dose of 1-2J/cm2; 2 – 3 sittings per week. The dose is then increased by 0.5 J/ cm2. [66] Side effects of this therapy include nausea, pruritus, epigastric discomfort, nervousness, erythema, blistering reaction, cataract and photocarcinogenesis. If there is no response after 6 months or 50 treatments, PUVA should be terminated. [66]

4. Phenylalanine with UVA exposure

It has been used orally and topically with UVA exposure. A 5% aqueous L- phenylalanine solution was orally administered 1 h before UVA irradiation. Using a cream containing 10 % L-phenylalanine over achromic areas 20 min before exposure gives better results. Irradiation was twice a week as per the above schedule for six months. The most common areas of repigmentation are the arms, legs, knees and eyelids and there are no side effects. [67]

5. **Khellin with UVA exposure**

   Khellin, a furanochrome isolated from the seeds of Ammi visnaga, a plant of the eastern Mediterranean area, has been effective a photosensitizer as psoralen. It is free from toxic side effects and well tolerated. [68]

6. **Excimer laser (308nm)**

   The 308nm xenon chloride excimer laser is an effective and safe modality for the treatment of chronic stable vitiligo, with good results achieved in short duration of time. Treatment given twice or thrice weekly for 10 to 15 sittings. Initial pigmentation is observed by 4 to 8 weeks. It acts through immunomodulation by affecting the T cells. Repigmentation occurs fastest with thrice weekly treatment. However treatment period more than 12 weeks is required. [69]

C. SURGICAL THERAPY

1. Only stable localized vitiligo lesions (segmental or non segmental vitiligo), unresponsive to other treatment modalities are chosen for surgical treatment.

2. Surgical procedures are not performed in very young children as segmental or stable focal lesions increase in size with body growth.

3. Moreover success of many procedures depends on postoperative immobility of the operated part, which is difficult to maintain in young children.

4. Older children and adolescents may be counselled about the procedure and possible outcome of the surgery to achieve their cooperation. The restrictive factors for surgery are inability to treat larger site and risk of koebnerisation of the donor site.

5. Among the various surgical techniques, suction blister epidermal grafting has been found to be the most convenient and effective for children, however prolonged immobility is required.

6. Non- cultured autologous epidermal transplantation has been used successfully in children and adolescents with stable vitiligo.

7. Cultured melanocyte transplantation is a relatively tedious technique requiring specialised set up, trained staff and a preparation time of 6 to 8 weeks. Cost may be a restrictive factor for poor families in availing this treatment modality. [34]

D. DEPIGMENTING THERAPY FOR EXTENSIVE VITILIGO.

Recalcitrant cases of widespread vitiligo or universal vitiligo with only few islands of normal skin may be considered for total depigmentation

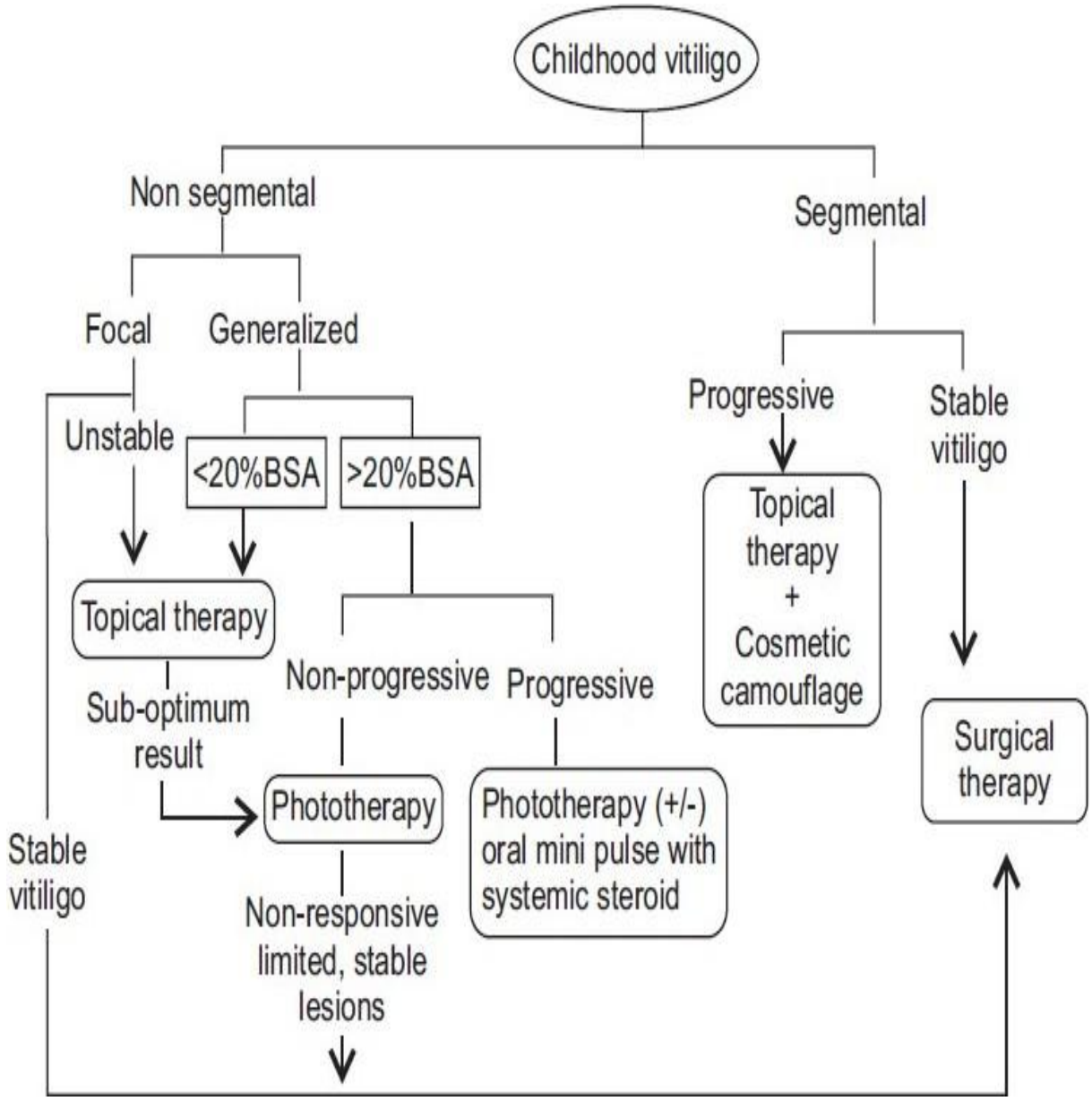
therapy with 20% monobenzyl ether of hydroquinone with an advice of lifelong stringent protection. [34]

E. COSMETIC CAMOUFLAGE.

Good quality cover-up cosmetics (available in commercial names: Dermablend, Covermark, Dermacolor) may be used to cover localised vitiligo lesions over exposed body parts in children. [34]

Treatment of vitiligo at any age remains a challenge, more so during childhood.

None of the available therapies is absolutely effective, and the disease runs a relapsing course. The art of treatment of childhood vitiligo is a fine balance between addressing all these issues and achieving the best result out of the available modalities. [34]



TREATMENT OF CHILDHOOD VITILIGO

TACROLIMUS

It is a macrolide immunosuppressant that comes from the fungus Streptomyces tsukubaensis, is a novel treatment for vitiligo. [5]

MECHANISM OF ACTION

- It binds to an immunophillin, FK binding protein (FKBP-12), located in the cytoplasm of T- lymphocytes. The complex formed inhibits the phosphatise calcineurin. This inhibition prevents signal transduction which ultimately halts the transcription of cytokines IL-2, IL-3, IL-4, IL -5, IL-8, GM-CSF, TNF-alpha and IF-gamma.
- It also causes inhibition of histamine release from skin mast cells.
- It causes impairment of synthesis of prostaglandin- D2.
- Down regulation of FCeR1 on langerhan's cells.
- Inhibition of CD4 and CD8 lymphocyte migration.

At molecular level proliferation of both melanocytes and melanoblasts is significantly enhanced by tacrolimus. The concentration of stem cell factor in keratinocyte supernatant increases in a dose dependent manner. [5]

PHARMACOKINETICS

Systemic absorption with topical tacrolimus is minimal. After single or multiple doses of 0.1% tacrolimus ointment peak blood concentrations

were in the range of 5-20 ng/ml. The absolute bioavailability of topical tacrolimus is unknown. The damaged skin has higher rate of percutaneous absorption. [5]

CONTRAINDICATION

In patients with history of hypersensitivity to tacrolimus.

ADVERSE EFFECTS

Burning sensation, stinging, soreness, pruritus.

DRUG INTERACTIONS. [5]

Based on minimum extent of absorption interaction of tacrolimus with systemically absorbed drugs are unlikely.

DOSAGE AND ADMINISTRATION. [5]

Tacrolimus ointment 0.03% for pediatric use and 0.1% for adults.

AIM OF THE STUDY

- The aim of the study is to compare the efficacy of 0.03% tacrolimus alone with 0.03% tacrolimus and mid-potent topical corticosteroids in the treatment of childhood vitiligo.

MATERIAL AND METHODS

Study design

0.03% tacrolimus alone

Versus

0.03% tacrolimus and topical mid-potent corticosteroids (mometasone furoate 0.1%)

This was a 2 year, randomized, open, prospective, parallel group, comparative study conducted in vitiligo patients attending the Vitiligo Clinic, Department of Dermatology, Government Chengalpattu medical college, Chengalpattu.

This study was conducted from November 2010 to October 2012. (2years).

50 patients in the age group 2 to 14 years were enrolled in the study.

During the initial visit the patients' demographic details including the name, age, sex, and residential address were noted.

A detailed history regarding the onset, duration and course of the disease, presence or absence of precipitating factors, family history, associated skin

and systemic problems, treatment taken so far and its outcome were recorded.

Dermatological assessment of the disease was carried out noting down the sites of involvement, total body surface area involved, total number of patches, size and distribution of the patches, presence of white hair in the patch.

Details regarding the margin of the patch, skin texture, presence or absence of perifollicular pigmentation, Koebner's phenomenon, associated other skin and systemic problems were noted. Focal sepsis was ruled out by referring the patient to ENT and Dental OPD for check up.

After collecting the preliminary reports the patient was assessed for eligibility for randomization. Randomization was performed according to computer generated random code. Treatment was identified by a code number either A or B according to treatment group.

Patients with code A received treatment with 0.03% tacrolimus alone and patients with code B received treatment with 0.03% tacrolimus and topical steroids.

The patients were asked to stick only to the study treatment as per the randomization code.

GROUP A	GROUP B
1	3
2	5
4	7
6	8
9	10
12	11
14	13
15	16
18	17
19	20
22	21
24	23
25	26
28	27
30	29
31	32
33	35
34	37
36	38
41	39
42	40
43	44
47	45
48	46
49	50

Inclusion criteria

1. Age more than 2 years and less than 14 years.
2. Children free of chronic illness and systemic diseases.
3. All types of vitiligo except vitiligo vulgaris irrespective of site and activity of the disease.

Exclusion criteria

1. Age less than 2 years and more than 14 years.
2. Chronic illness like tuberculosis and lymphoproliferative diseases.
3. Those children previously treated or at present treated with alternate system of medicine.
4. Vitiligo involving more than 20% BSA.

ADMINISTRATION OF STUDY TREATMENT

- Patients with code A were advised to use 0.03% tacrolimus ointment twice daily morning and night.
- Patients with code B were advised to use 0.03% tacrolimus morning and topical steroid mometasone furoate 0.1% at night for 2 months continuously with a gap of 1 week from subsequent application to reduce the side effects associated with topical steroids. However 0.03%

tacrolimus was applied in the morning continuously unlike topical steroids.

- As with any topical application patients and caregivers were advised to wash hands after application.
- Patients should minimize exposure to natural or artificial sunlight.
- Patients should report any signs of adverse reactions to the physician.
- Before application of the ointment the skin must be completely dry.
- Total duration of study was 2 years. During the study period of 2 years patients were followed up every 2 weeks and improvement was assessed at the end of 1 year with the help of photographs.
- Any adverse effects during the study were recorded with importance to erythema and systemic side effects. If any adverse effects were observed then its severity, onset, course, action taken and relationship to study drug were recorded.

EFFICACY PARAMETERS

The primary efficacy variable was the percentage change in depigmentation from baseline to the end of study period.

The secondary efficacy parameters include the Physician's Global Improvement assessment and Patient Global Inprovement assessment which was computed at the end of the study.

During the initial assessment, estimation of body surface area (BSA) involvement was assessed using Vitiligo Area Scoring Index (VASI). The body was divided into the following mutually exclusive regions:

1) Face and Neck, upper limbs (excluding hands), lower limbs (excluding feet).
2) Hands and feet.
3) Genitalia and
4) Trunk.

Buttocks were included with the lower extremities.

One hand unit, which encompasses the palm plus the volar surface of all the digits is approximately 1% of total body surface area and was used as a guide to estimate the baseline percentage of vitiligo involvement of any body region. To eliminate variation in hand size, we defined a hand unit to be the volar hand, including the fingers of single investigator.

All the patients were followed up once in every two weeks, to look for any macular repigmentation, presence of new lesions and presence of adverse effects. At each follow up assessment the extent of residual depigmentation within each affected patch which had been present at baseline was estimated to the nearest of one of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. Any new depigmented patches that developed

during the study were also estimated using the hand unit method and were included in the VASI calculation. For each body region the VASI was determined by the product of the area of vitiligo in hand units (which were set at 1% per unit) and the extent of depigmentation within each hand unit measured patch.

Standardized assessment for estimating the degree of pigmentation to derive the Vitiligo Area Scoring Index (VASI).

- At 100% depigmentation, No pigment is present.
- At 90%, specks of pigment are present.
- At 75%, the depigmented area exceeds the pigmented area.
- At 50%, the depigmented area and the pigmented area are equal.
- At 25%, the pigmented areas exceed the depigmented area.
- At 10%, only specks of depigmentation are present.

Total body VASI was then calculated using the following formula:-

Total Body VASI = $\Sigma^{\text{All bodysites}}$ [hand units X residual depigmentation]

Clinical photographs were taken at baseline and at each monthly follow up visits as an aid to the Global clinical scoring. VASI was determined by direct clinical examination.

The Physician's Global improvement assessment evaluated the overall change from baseline in VASI score on a 5 point scale.

Score Improvement in % Comments

1. 76% - 100%. Excellent improvement.
2. 51% - 75%. Marked improvement.
3. 26% - 50%. Definite improvement.
4. 1% - 25%. Minimal improvement.
5. 0%. No change

Patient's Global assessment was evaluated based on the response to the treatment as perceived by the patient with or without comparison to previous treatment if any. This was assessed in a 4 point scale.

1. Much better.
2. Slightly better.
3. Same.
4. Worse.

Primary efficacy parameter, VASI was assessed at baseline and then in two months during follow up for 12 months and Secondary efficacy parameters Physician's Global assessment and Patient's Global assessment were evaluated only at the end of 12 months.

STATISTICAL ANALYSIS

The statistical analysis was carried out using statistical software STATA 6.0.

The Categorical variables were expressed as Frequency and percentage. The Quantity variables were expressed as mean and standard deviation. Descriptive statistics were used to evaluate baseline characteristics and adverse effects.

The group comparison for the categorical variables were analysed using Chi square test and for quantity variables were analysed using unpaired students ‘t’ test.

The change from baseline of efficacy parameters within each treatment group was evaluated using the student t-test. The p value of less than 0.05 was considered as statistically significant.

OBSERVATION

A total of 50 patients were enrolled in the study, with 25 patients randomized to receive treatment with 0.03% tacrolimus only and 25 patients to receive treatment with 0.03% tacrolimus and topical steroids. All 50 patients were included in the safety population.

Type	**Tacrolimus**		**Tacrolimus with Steroids**		**Total**
	Female	**Male**	**Female**	**Male**	
Completed	12	12	11	12	**47**
Drop Out	0	1	1	1	**3**
Total	**12**	**13**	**12**	**13**	**50**

Out of these 50 patients, 47 patients completed the study for the period of 1year. Three of these patients, 1 in the tacrolimus group and 2 in the tacrolimus with topical steroids group, discontinued the study and their efficacy data was not included in the analysis. Most of the drop outs are between 8 to 12 weeks after commencing the treatment.

Age Distribution

Age	Tacrolimus	Tacrolimus with Steroids	Total
2-5 yrs	2	1	3
6-10 yrs	13	19	32
11-14 yrs	9	3	12
Total	24	23	47

Out of the 25 patients enrolled for tacrolimus only(group A) treatment, 13 were in the age group of 6 to 10yrs. Out of the 25 patients enrolled for tacrolimus and topical corticosteroids(group B) 19 were in the age group of 6 to 10yrs.

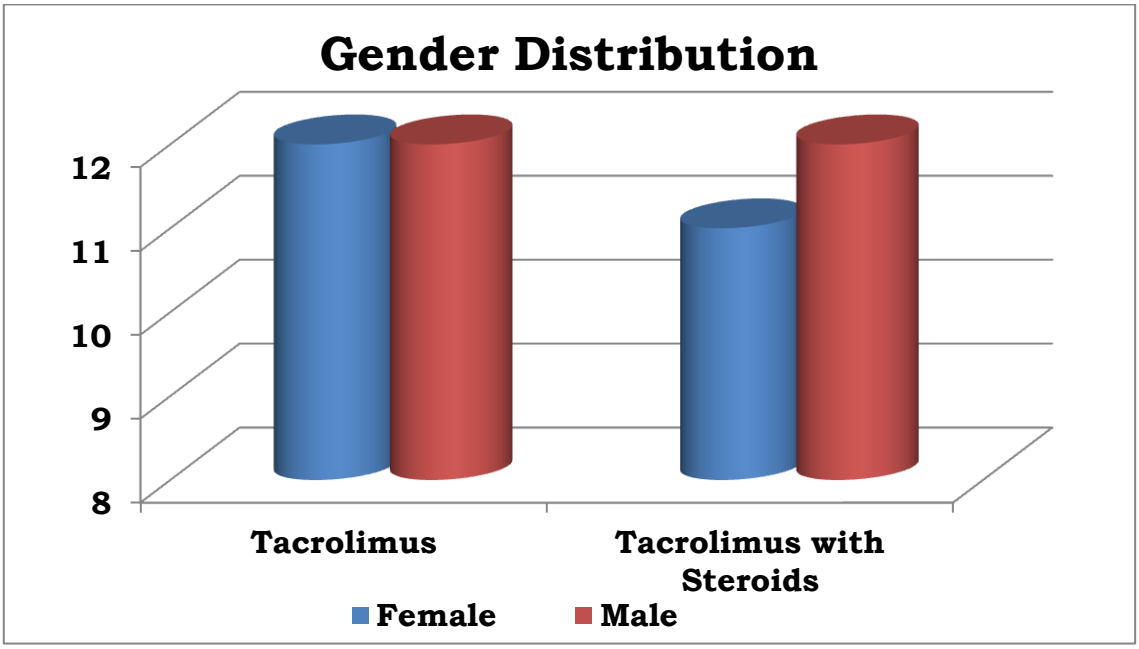
Variable	Tacrolimus	Tacrolimus with Steroids
Age*	9.25 $\pm$ 2.63	8.96 $\pm$ 1.94

*Values are expressed as Mean $\pm$ S.D

There is no significance difference between the Age distribution among the Tacrolimus and Tacrolimus with Steroids, p value >0.05.

Sex Distribution

Sex	Tacrolimus	Tacrolimus with Steroids	Total
Female	12	11	23
Male	12	12	24
Total	24	23	47

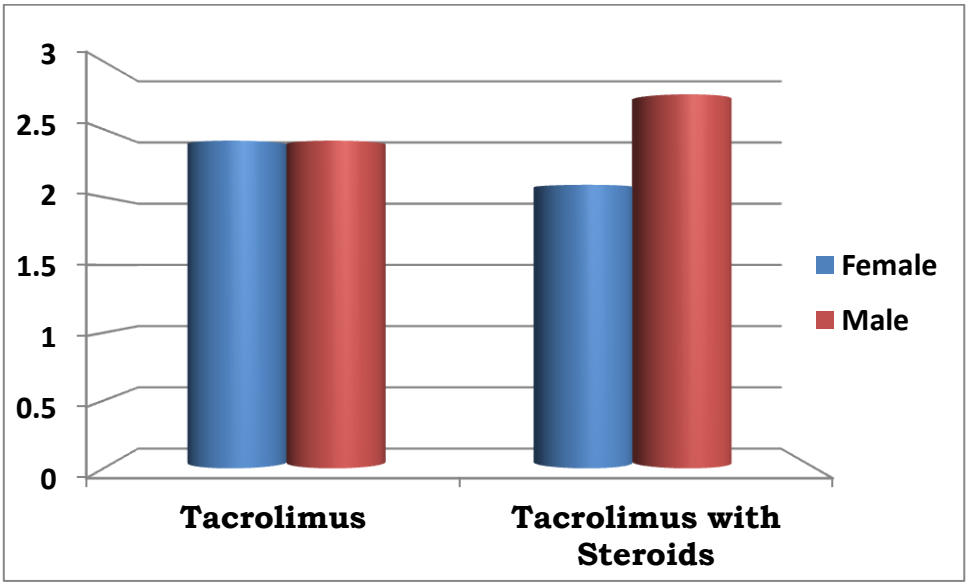


Out of the 25 patients enrolled for group A treatment, 12 were Males and other 12 were Females. Out of the 25 patients enrolled for group B treatment, 12 were Males and 11 were Females.

Since P= .882 (>0.05).There is no statistical significant difference between the sex distribution among the Tacrolimus and Tacrolimus with Steroids

Duration of disease

Duration of Disease	Tacrolimus	Tacrolimus with Steroids
Total	2.4166 yrs (n=24)	2.4391yrs (n=23)
Female	2.4166 yrs (n=12)	2.0909 yrs (n=11)
Male	2.4166 yrs (n=12)	2.7583 yrs (n=12)

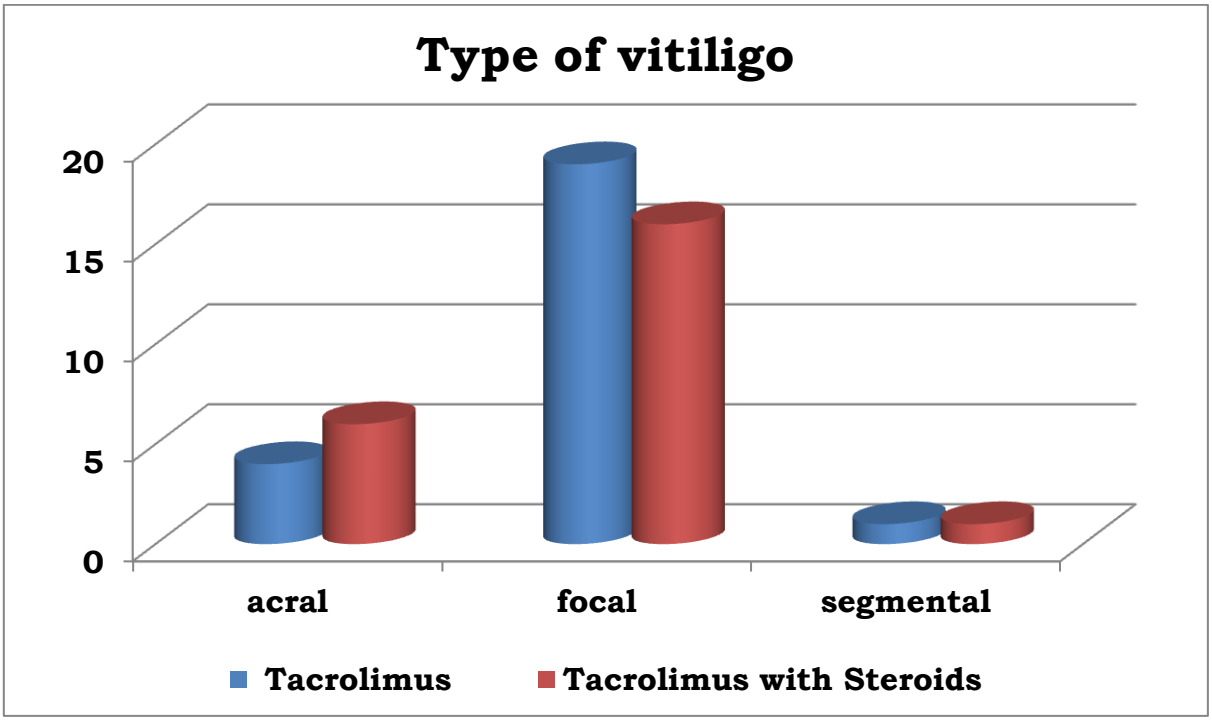


The mean duration of vitiligo was 2.416 yrs in patients enrolled for Group A and 2.491 yrs in the group B.

Type of Vitiligo

Type	Tacrolimus		Tacrolimus with Steroids		Total
	Female	Male	Female	Male	
Acral	0	4	1	5	10
Focal	12	7	9	7	35
Segmental	0	1	1	0	2
Total	**12**	**12**	**11**	**12**	**47**

18 patients with focal vitiligo, 1 with segmental vitiligo, and 4 with acral vitiligo were included in tacrolimus only treated group. 8 with focal vitiligo and 14 with acral vitiligo were included in the tacrolimus and topical corticosteroids group.



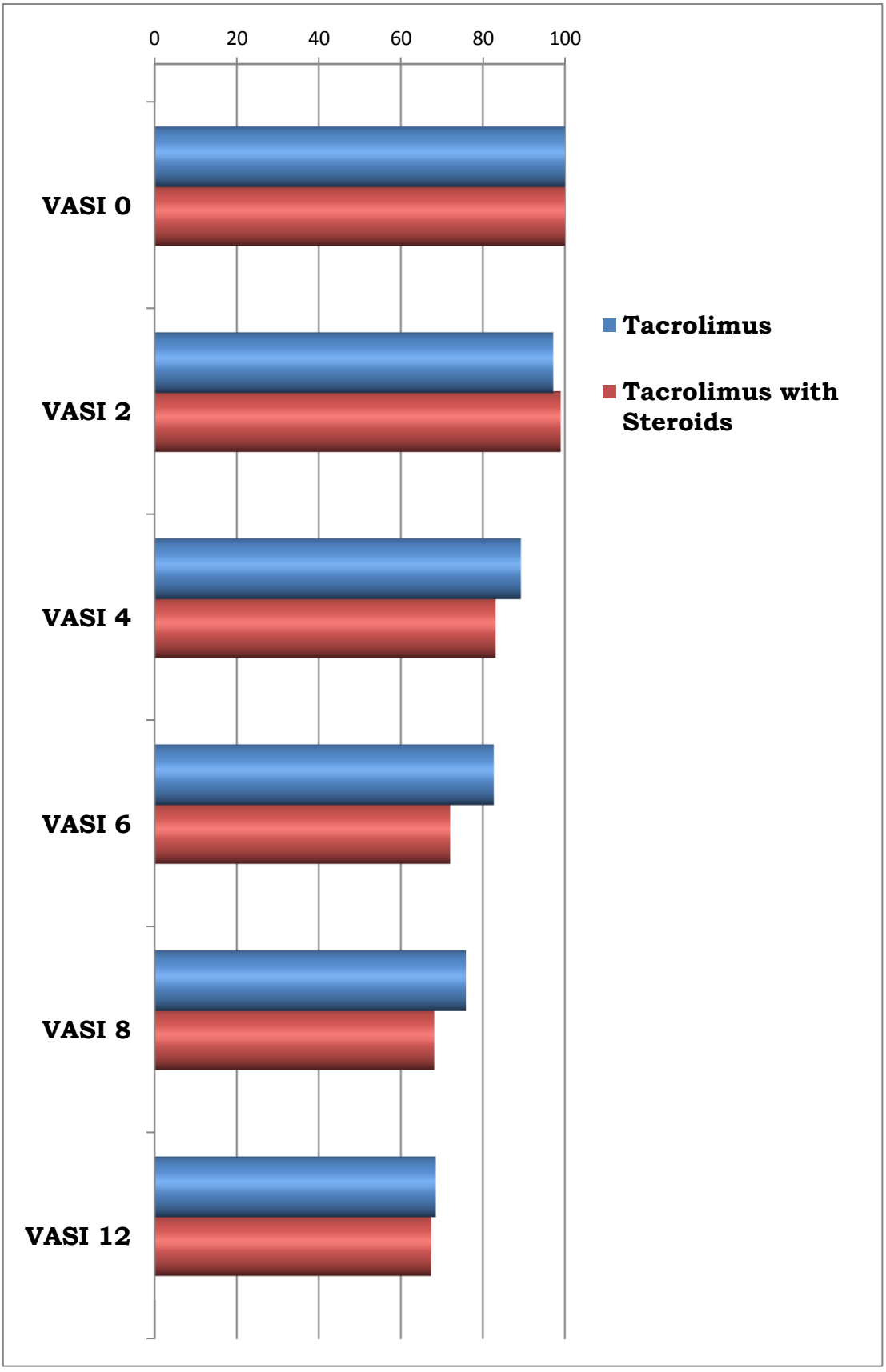
Total Body VASI Reduction

Total Body VASI Reduction	Tacrolimus	Tacrolimus with Steroids
VASI 0	0.1988 (100%)	0.6154 (100%)
VASI 2	0.1931 (97.14%)	0.6091 (98.98%)
VASI 4	0.1775 (89.28%)	0.5113 (83.08%)
VASI 6	0.1644 (82.68%)	0.4433 (72.04%)
VASI 8	0.1508 (75.87%)	0.4194 (68.15%)
VASI 12	0.1363 (68.53%)	0.4151 (67.45%)

The mean total body VASI in Tacrolimus group at baseline was 0.1988 (Taken as 100%) and in Tacrolimus with steroid group it was 0.6154 (100%) with a p value <0.05 which is statistically significant.

The mean total body VASI in Tacrolimus group at the end of 2 month was 0.1931 (97.14%) and in Tacrolimus with steroid group it was 0.6091(98.98%) with a p value <0.05 which is statistically significant. It shows that the onset of action was earlier in tacrolimus and topical corticosteroids group.

The mean total body VASI after 12 months of therapy with Tacrolimus alone was 0.1363 (68.53%) and in Tacrolimus with steroid group it was 0.4151 (67.45%) with a p value <0.05 which is statistically significant.

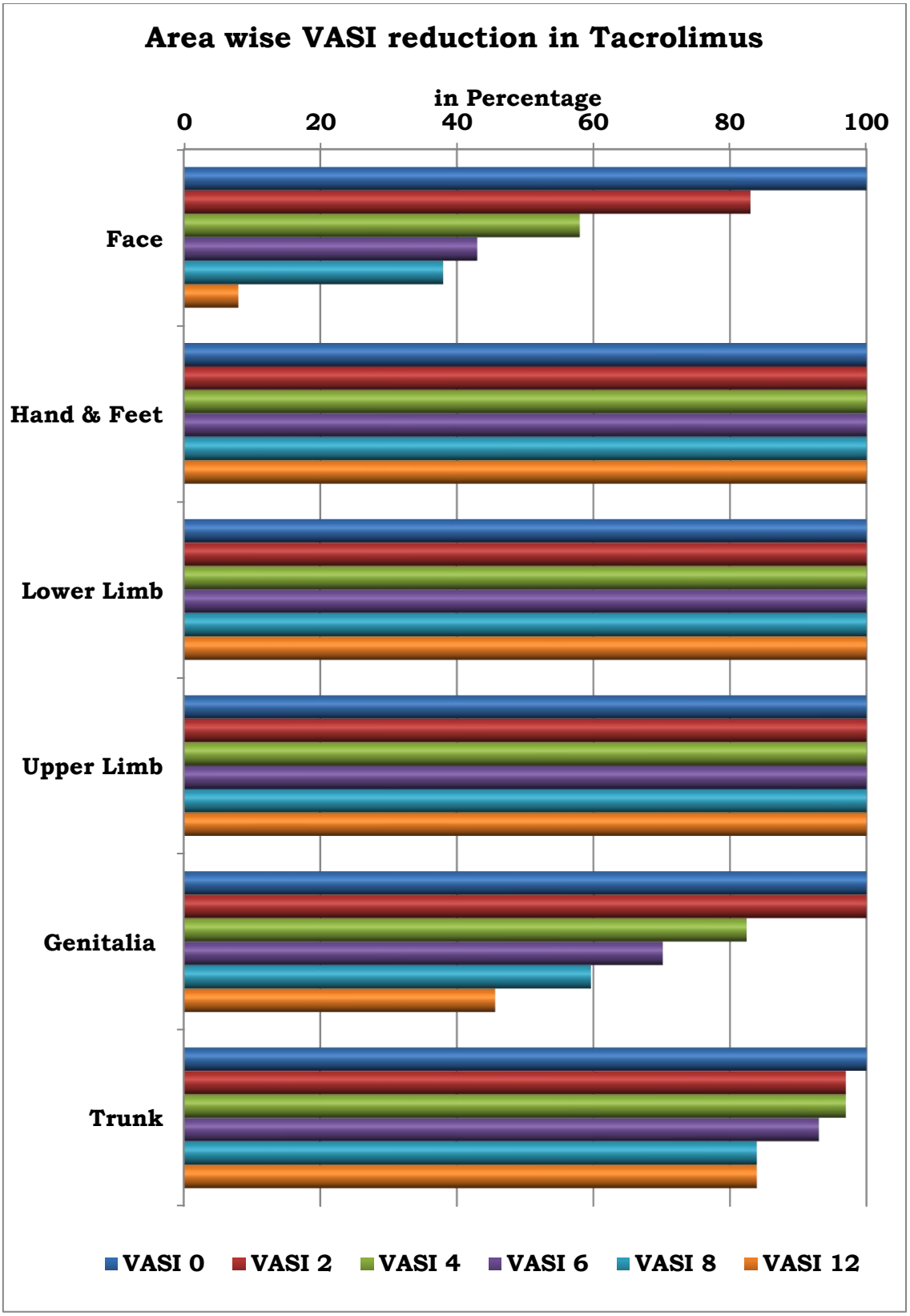

0
20
40
60
80
100
VASI 0
VASI 2
VASI 4
VASI 6
VASI 8
VASI 12
Tacrolimus
Tacrolimus with Steroids

Area wise VASI reduction in Tacrolimus

Area Wise VASI Reduction	Face	Hands & Feet	Lower Limb	Upper Limb	Genitalia	Trunk
VASI 0m	0.1000 **(100%)**	0.1900 **(100%)**	0.3750 **(100%)**	0.0600 **(100%)**	0.2375 **(100%)**	0.2357 **(100%)**
VASI 2m	0.0830 **(83%)**	0.1900 **(100%)**	0.3750 **(100%)**	0.0600 **(100%)**	0.2375 **(100%)**	0.2286 **(96.97%)**
VASI 4m	0.0580 **(58%)**	0.1900 **(100%)**	0.3750 **(100%)**	0.0600 **(100%)**	0.1958 **(82.46%)**	0.2286 **(96.97%)**
VASI 6m	0.0430 **(43%)**	0.1900 **(100%)**	0.3750 **(100%)**	0.0600 **(100%)**	0.1667 **(70.18%)**	0.2193 **(93.03%)**
VASI 8m	0.0380 **(38%)**	0.1900 **(100%)**	0.3750 **(100%)**	0.0600 **(100%)**	0.1417 **(59.65%)**	0.1979 **(83.94%)**
VASI 12m	0.0080 **(8%)**	0.1900 **(100%)**	0.3750 **(100%)**	0.0600 **(100%)**	0.1083 **(45.61%)**	0.1979 **(83.94%)**

The area wise VASI reduction in tacrolimus is as follows:-

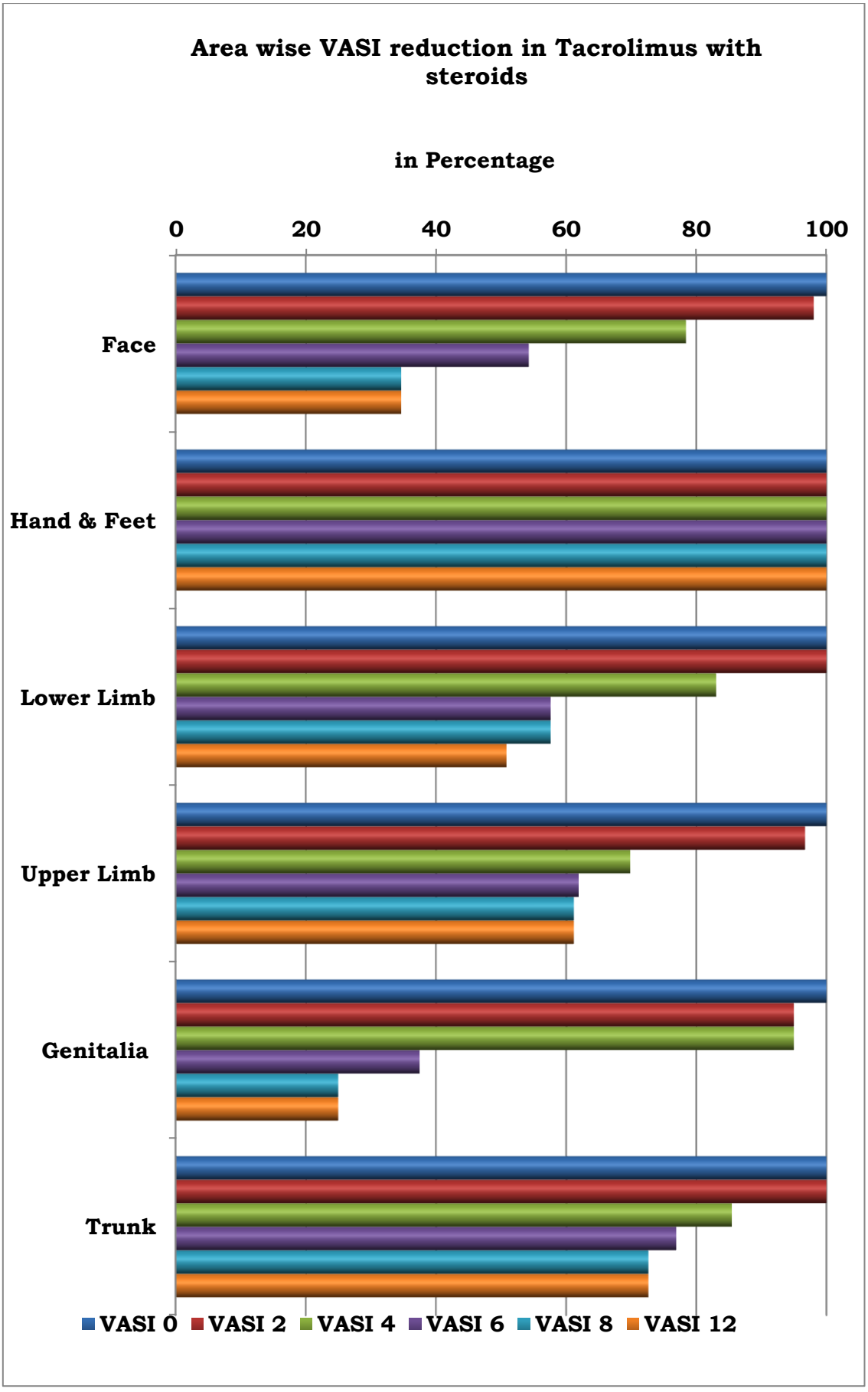
Face – 92 %, genitalia - 54.39 %, trunk - 16.06 %, upper limbs, lower limbs, hands and feet – 0 %.


Area wise VASI reduction in Tacrolimus
in Percentage
0
20
40
60
80
100
Face
Hand & Feet
Lower Limb
Upper Limb
Genitalia
Trunk
VASI 0
VASI 2
VASI 4
VASI 6
VASI 8
VASI 12

Area wise VASI reduction in Tacrolimus and topical steroids.

Area Wise VASI Reduction	**Face**	**Hand & Feet**	**Lower Limb**	**Upper Limb**	**Genitalia**	**Trunk**
VASI 0m	0.4250 **(100%)**	0.3342 **(100%)**	0.3688 **(100%)**	0.8375 **(100%)**	0.1000 **(100%)**	1.1465 **(100%)**
VASI 2m	0.4167 **(98.04%)**	0.3342 **(100%)**	0.3688 **(100%)**	0.8100 **(96.72%)**	0.0950 **(95%)**	1.1465 **(100%)**
VASI 4m	0.3333 **(78.43%)**	0.3342 **(100%)**	0.3063 **(83.05%)**	0.5850 **(69.85%)**	0.0950 **(95%)**	1.1250 **(85.47%)**
VASI 6m	0.2307 **(54.27%)**	0.3342 **(100%)**	0.2125 **(57.63%)**	0.5188 **(61.94%)**	0.0375 **(37.50%)**	1.1250 **(76.92%)**
VASI 8m	0.1473 **(34.67%)**	0.3342 **(100%)**	0.2125 **(57.63%)**	0.5125 **(61.19%)**	0.0250 **(25%)**	1.0625 **(72.65%)**
VASI 12m	0.1473 **(34.67%)**	0.3342 **(100%)**	0.1875 **(50.85%)**	0.5125 **(61.19%)**	0.0250 **(25%)**	1.0625 **(72.65%)**

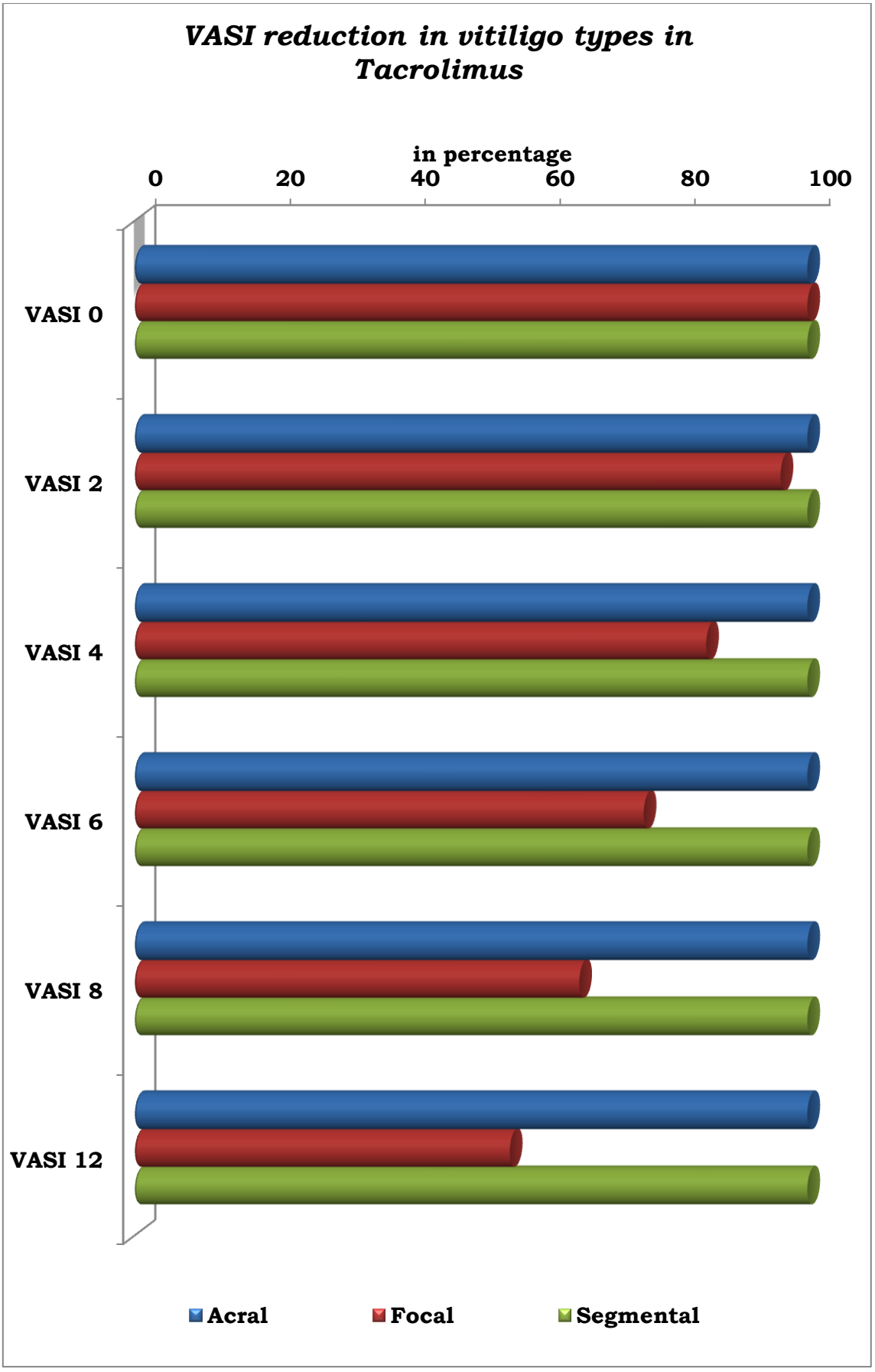
The area wise VASI reduction in tacrolimus and topical steroids treated group is as follows: - Genitalia - 75% face - 65.33%, lower limbs-49.15%, upper limbs - 38.89 %, trunk - 27.35%, hands and feet - 0%.


Area wise VASI reduction in Tacrolimus with steroids
in Percentage
0
20
40
60
80
100
Face
Hand & Feet
Lower Limb
Upper Limb
Genitalia
Trunk
VASI 0
VASI 2
VASI 4
VASI 6
VASI 8
VASI 12

VASI Reduction in Vitiligo Type in Tacrolimus

VASI reduction (at months)	Acral	Focal	Segmental
VASI 0m	0.24875(100%)	0.17895 (100%)	0.375 (100%)
VASI 2m	0.24875(100%)	0.17184(96.03%)	0.375 (100%)
VASI 4m	0.24875(100%)	0.15211(85%)	0.375 (100%)
VASI 6m	0.24875(100%)	0.13553(75.73%)	0.375 (100%)
VASI 8m	0.24875(100%)	0.11842(66.17%)	0.375 (100%)
VASI 12m	0.24875(100%)	0.1(55.88%)	0.375 (100%)

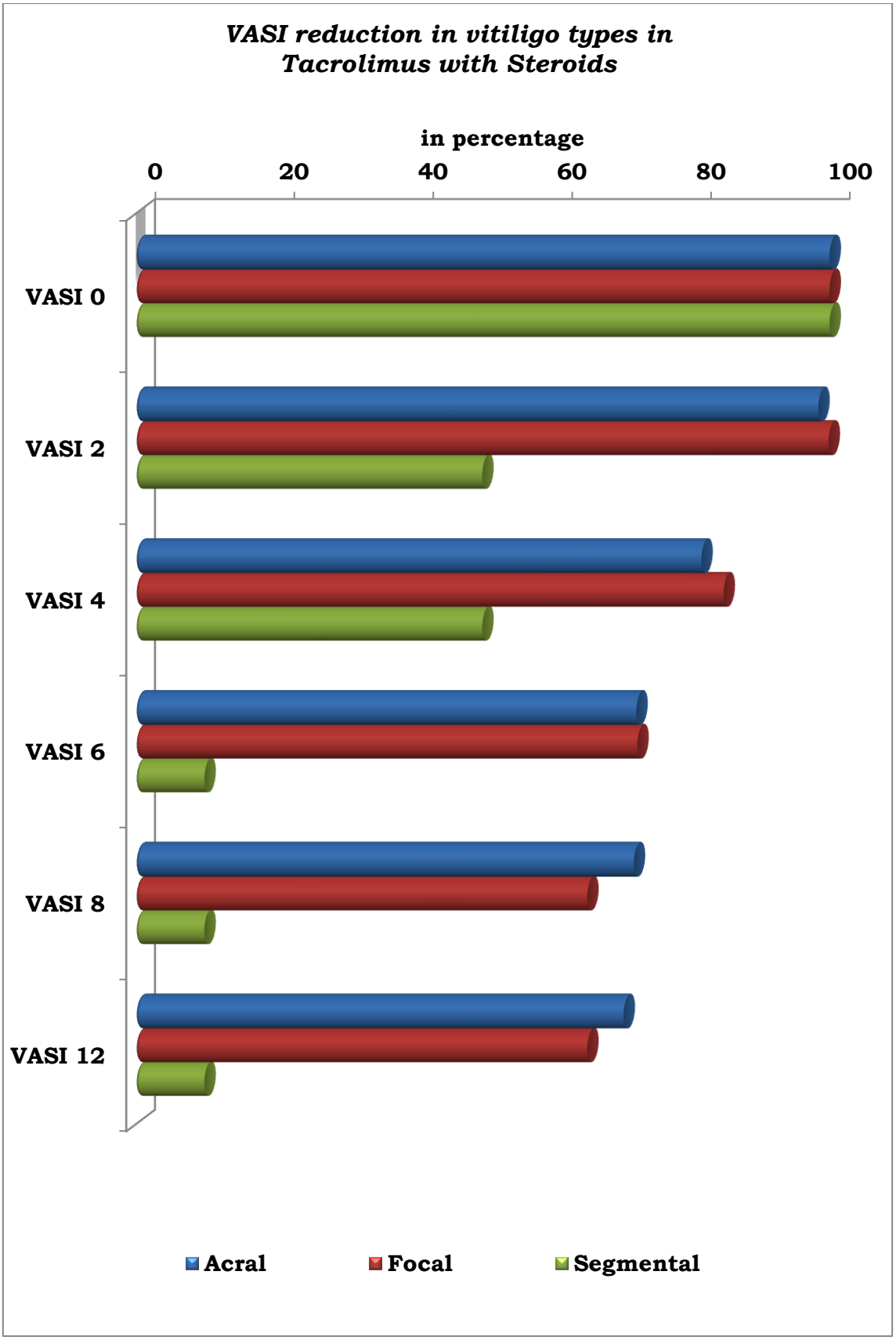
The VASI reduction in vitiligo types of tacrolimus only group was noted as follows: - focal vitiligo 44.12%, segmental vitiligo 0%, and acral vitiligo 0%.


VASI reduction in vitiligo types in Tacrolimus
in percentage
0
20
40
60
80
100
VASI 0
VASI 2
VASI 4
VASI 6
VASI 8
VASI 12
Acral
Focal
Segmental

VASI Reduction in Vitiligo Type in Tacrolimus with Steroids

VASI reduction (at months)	Acral	Focal	Segmental
VASI 0m	0.4879 (100 %)	0.90938(100%)	0.05(100%)
VASI 2m	0.48 (98.38%)	0.90813(99.865%)	0.025(50%)
VASI 4m	0.39786(81.55%)	0.77063(84.74%)	0.025(50%)
VASI 6m	0.35214(72.18%)	0.65775(72.33%)	0.005(10%)
VASI 8m	0.35036(71.81%)	0.59213(65.11%)	0.005(10%)
VASI 12m	0.34321(70.35%)	0.59213(65.11%)	0.005(10%)

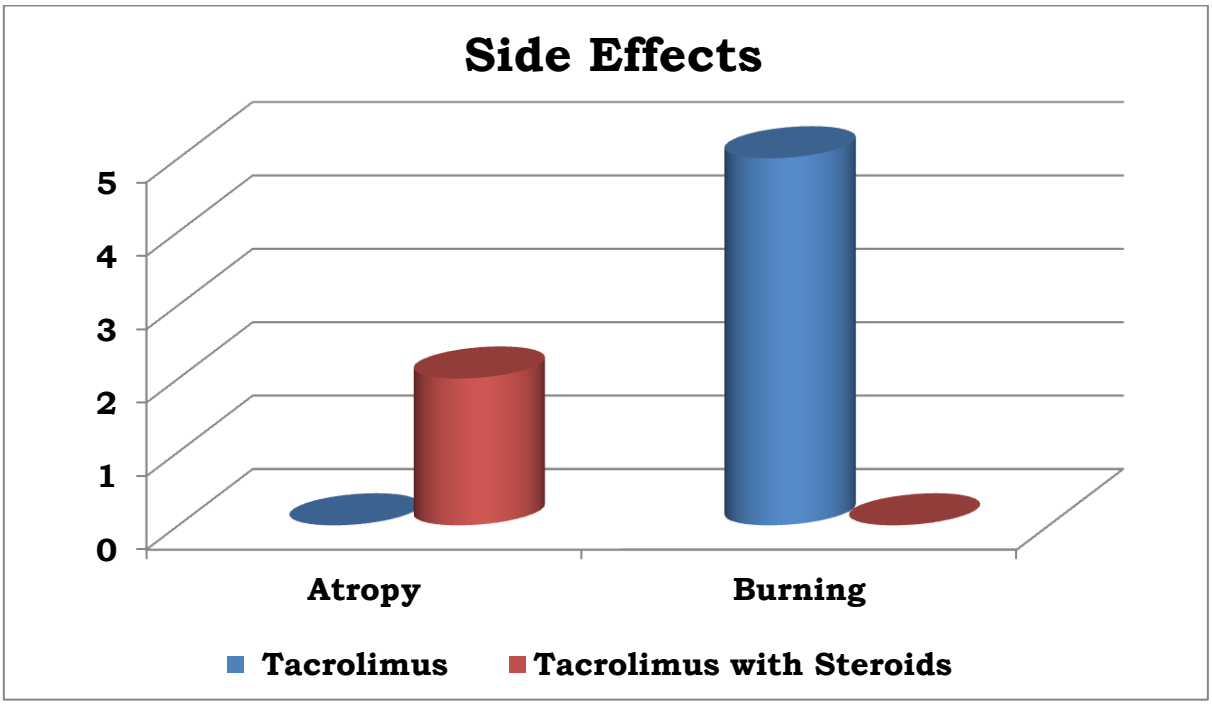
The VASI reduction in vitiligo types of tacrolimus with topical steroids group was as follows: segmental vitiligo 90%, focal vitiligo 34.89%, and acral vitiligo 29.65%.


VASI reduction in vitiligo types in Tacrolimus with Steroids
in percentage
0
20
40
60
80
100
VASI 0
VASI 2
VASI 4
VASI 6
VASI 8
VASI 12
Acral
Focal
Segmental

Adverse Effects

Effects	Tacrolimus	Tacrolimus with Steroids	Total
Atrophy	0	2	2
Burning	5	0	5
Total	5	2	7

Side effects included mainly burning sensation in about 5 patients in tacrolimus only treated group where as in tacrolimus with steroid group it included atrophy in about 6 patientsts.

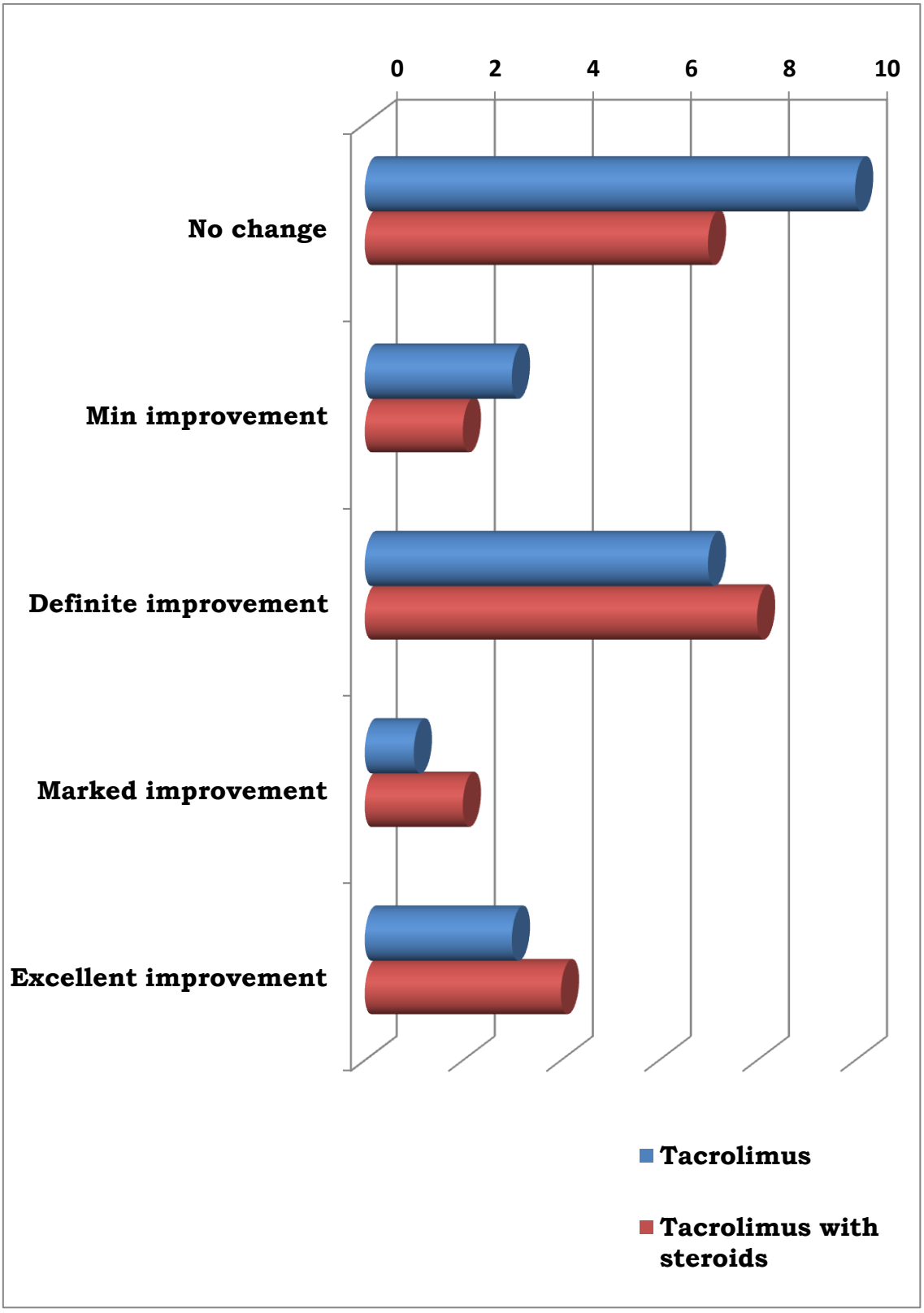


Total reduction in VASI: Physician's Global assessment:

			Tacrolimus		Tacrolimus with steroids	
Score	**Comment**		**No of pts**	**%**	**No of pts**	**%**
5	**No change**	**0%**	**10**	**41.67**	**7**	**30.45**
4	**Min improvement**	**1-25%**	**3**	**12.5**	**2**	**8.69**
3	**Definite improvement**	**26-50%**	**7**	**29.16**	**8**	**34.78**
2	**Marked improvement**	**51-75%**	**1**	**4.16**	**2**	**8.69**
1	**Excellent improvement**	**76-100%**	**3**	**12.5**	**4**	**17.39**

The mean physician's global assessment score was 3.041 in Tacrolimus group and it was 3.261 in Tacrolimus with steroids group (**P value 0.657).** Physician's global assessment clearly showed that only 29.16% of patients treated with Tacrolimus alone had definite improvement whereas 34.78% of patients treated by Tacrolimus with steroids had definite improvement. Physician's global assessment clearly showed that only 12.5% of patients treated with Tacrolimus alone had excellent improvement whereas 17.39% of patients treated by Tacrolimus with steroids had excellent improvement.

Total reduction in VASI: Physician‘s Global Assessment.



Patient global assessment score

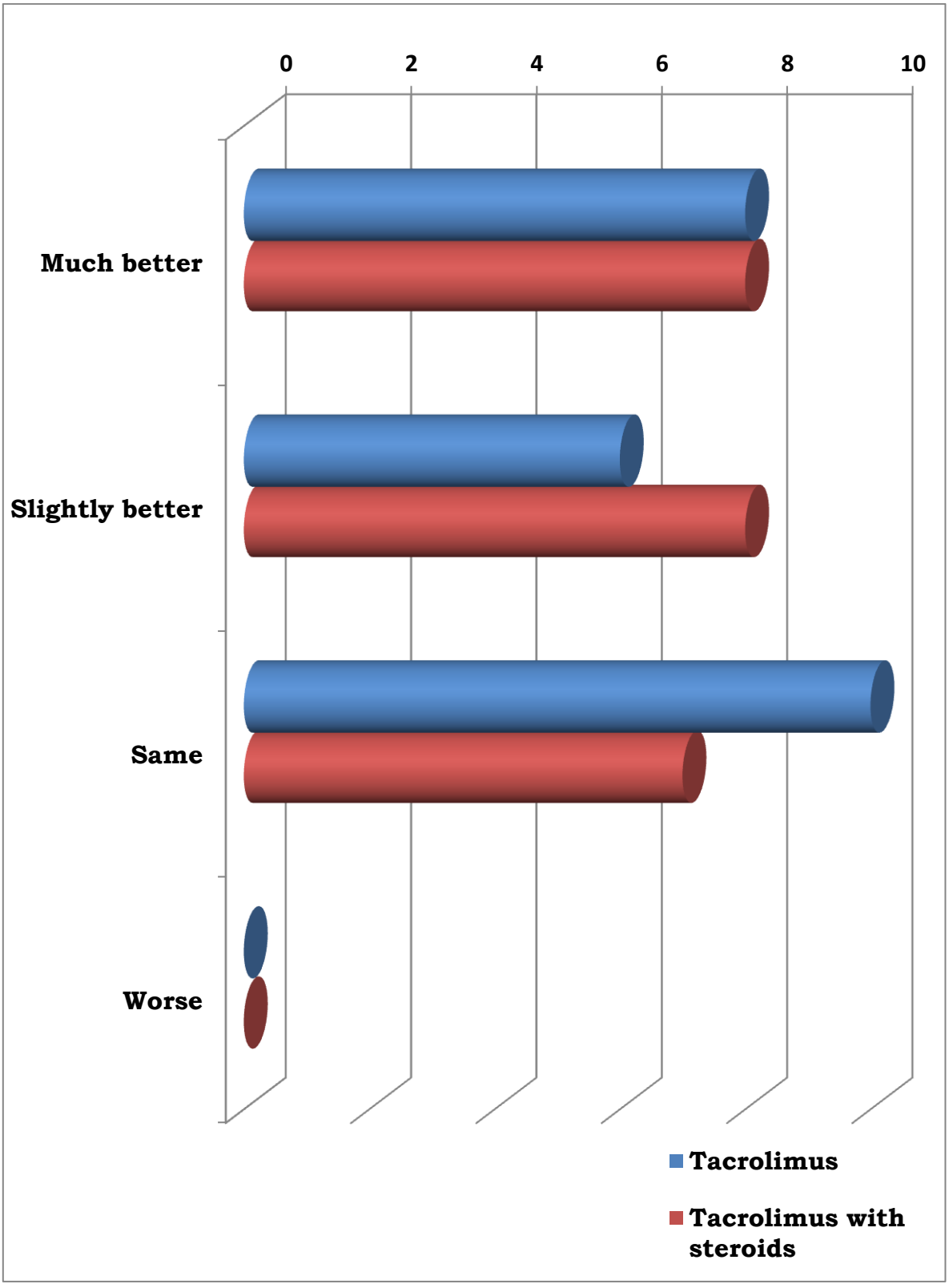
		Tacrolimus		**Tacrolimus with steroids**	
Score	**comment**	**No of pts**	%	**No of pts**	%
1	Much better	8	33.34%	8	34.78%
2	Slightly better	6	25%	8	34.78%
3	Same	10	41.67%	7	30.43%
4	Worse	0	0%	0	0

The mean patient global assessment score was 2.083 in Tacrolimus group and it was 1.957 in Tacrolimus with steroids group.

Patient global assessment clearly showed that only 33.34% of patients treated with Tacrolimus alone had much better improvement whereas 34.78% of patients treated by Tacrolimus with steroids had much better improvement.

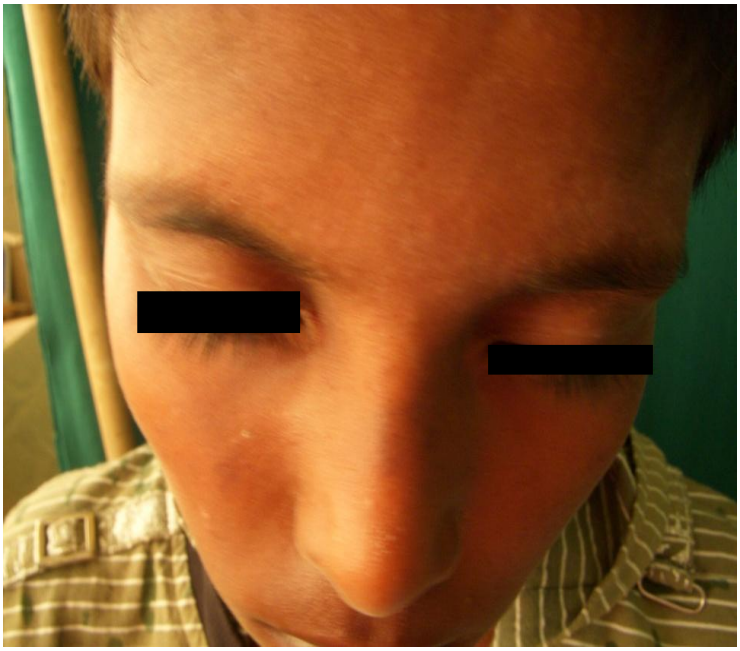
Patient global assessment clearly showed that 41.67%of patients treated with Tacrolimus alone had much better improvement whereas 30.43% of patients treated by Tacrolimus with steroids had no change.

Patient global assessment score



GROUP-A 0.03% TACROLIMUS ONLY

PRE-TREATMENT



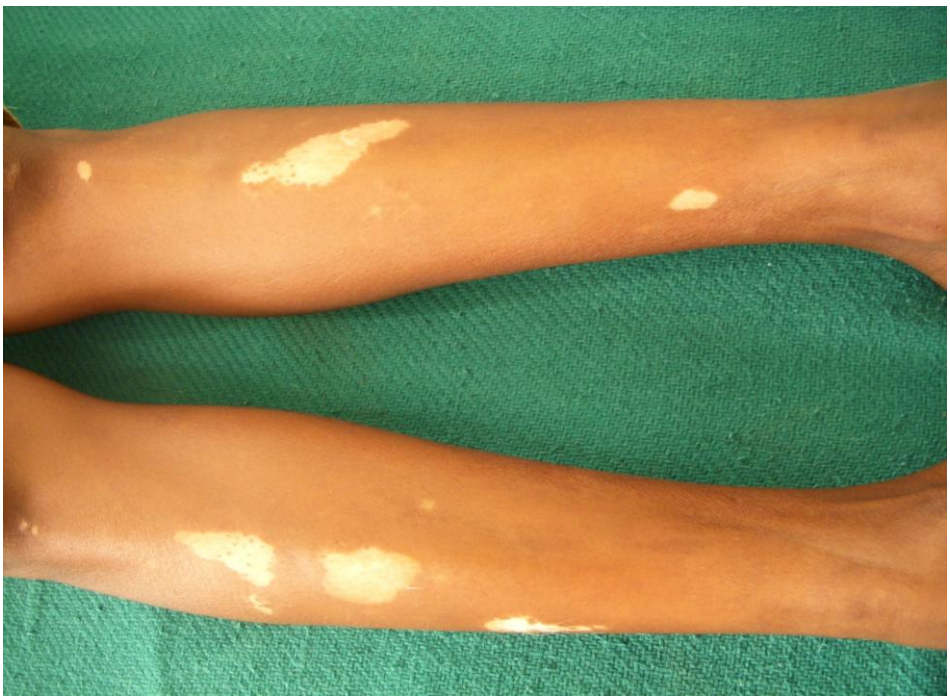
POST-TREATMENT

GROUP-A 0.03% TACROLIMUS ONLY

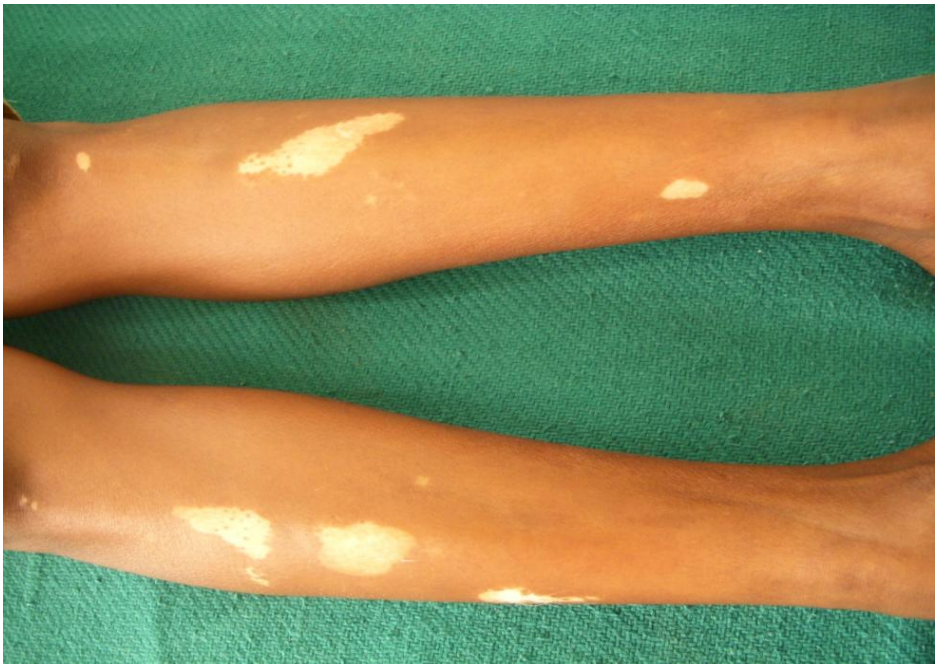
PRE- TREATMENT

POST- TREATMENT

GROUP-A 0.03% TACROLIMUS ONLY



PRE-TREATMENT



POST-TREATMENT

GROUP-A 0.03% TACROLIMUS ONLY

PRE-TREATMENT

POST-TREATMENT

GROUP-B 0.03% TACROLIMUS AND TOPICAL STEROIDS

PRE- TREATMENT

POST TREATMENT

GROUP-B 0.03% TACROLIMUS AND TOPICAL STEROIDS

PRE-TREATMENT

POST-TREATMENT

GROUP-B 0.03% TACROLIMUS AND TOPICAL STEROIDS

PRE-TREATMENT

POST-TREATMENT

GROUP-B 0.03% TACROLIMUS AND TOPICAL STEROIDS

PRE-TREATMENT

POST-TREATMENT

GROUP-B 0.03% TACROLIMUS AND TOPICAL STEROIDS

PRE-TREATMENT

POST-TREATMENT

DISCUSSION

This clinical comparative trial explored the efficacy of 0.03% tacrolimus(T) alone in comparison with 0.03% tacrolimus with topical corticosteroids (mometaone furoate) (T+S) in patients suffering from vitiligo less than 10% of body surface area involvement.

The baseline demographic data and baseline characteristics in both study groups, when compared were similar.

To our limited knowledge, there are no previous studies comparing the efficacy of 0.03% tacrolimus alone versus 0.03% tacrolimus and topical steroids.

The overall efficacy of 0.03% tacrolimus with topical corticosteroids (mometasone furoate) is slightly greater than 0.03% tacrolimus alone after the end of 12months with better response at 4 months in the former. This shows that 0.03% tacrolimus can be effectively used as topical monotherapy in patients with localized stable vitiligo.

However patients in group of 0.03% tacrolimus with topical corticosteroids showed significant reduction in total body VASI score in 4 months when compared 0.03% tacrolimus alone.

The reduction in former group is 16.92% when compared to 10.72% in latter group at 4 months of study period. This clearly shows that significant

repigmentation occurs earlier in patients treated with 0.03% tacrolimus with topical corticosteroids.

Patients with focal vitiligo and segmental vitiligo showed better clinical response to 0.03% tacrolimus with topical corticosteroids.

Patients with acral vitiligo did not respond to Tacrolimus or Tacrolimus and topical corticosteroids.

Facial vitiligo responded better with tacrolimus alone.
Genital vitiligo responded better to Tacrolimus and topical steroids as more female children were treated with combination than the male children.

Vitiligo involving the upper limb and lower limbs showed better response with Tacrolimus and steroids and minimal response with Tacrolimus only.

The secondary efficacy parameters like Physician's Global Assessment show results in favour of Tacrolimus and topical steroids treated group.

Apart from transient burning, no serious adverse effects were noted in T group. Atrophy was noted in Tacrolimus and topical steroids group.

There were hyperpigmented borders seen in patients treated with Tacrolimus and steroids which did not occur in patients treated with tacrolimus alone which showed homogenous pigmentation.

During the follow up period of three months after completion of the study, none of the patients in both study groups showed clinical signs of relapse evidenced by the fact that VASI remains the same as that of 12 months.

Small sample size, lack of placebo control and shorter duration of study were the major pitfalls in this study.

CONCLUSION

- 0.03 % Tacrolimus alone can be effectively used as topical monotherapy for treating localized stable Vitiligo.
- Facial vitiligo responds well to 0.03% tacrolimus alone and no need to add steroids topically as it increases the risk of atrophy.
- When midpotent topical corticosteroids are combined with tacrolimus there was significant reduction in VASI score at an earlier date, when compared to tacrolimus alone.
- The overall efficacy of tacrolimus with steroids is 32.55%, which was only slightly higher than tacrolimus only 31.47%.
- Acral vitiligo does not respond to tacrolimus alone or tacrolimus with topical corticosteroids.
- When midpotent topical corticosteroids are combined with tacrolimus was most effective in focal and segmental vitiligo.
- Vitiligo involving the upper limb and lower limbs showed better response with T+S.
- Tacrolimus alone was safe as there were no serious systemic or cutaneous adverse effects apart from transient burning in a few patients unlike steroids which caused atrophy in few patients.

BIBLIOGRAPHY

1. Sehgal VN, Srivastava G. Vitiligo: Compedium of clinicoepidemiological features. Indian J Dermatol Venerol Leprol 2007; 73:149-56.
2. Lancovelli P, Sinagara JL, Vidolin AP, Marenda S, Capitanio B, Leone G, et al. Relevance of thyroiditis and other autoimmune diseases in children with vitiligo.
3. Mazereeuw – Hautier J, Harper J. Vitiligo. In Harper J, Oranje A, Prose N editors. Textbook of pediatric dermatology. 2nd ed. Oxford: Blackwell Publishing Ltd; 2006. P. 1041-56.
4. Tamesis ME, Morelli JG. Vitiligo treatment in childhood: A state of the art review. Pediatr Dermatol 2010;27:437-45.
5. Lotti et al Vitiligo: new and emerging treatments Dermatologic therapy, Vol 21, 2008, 110-117.
6. Lerner AB. Vitiligo. J Invest Dermatol . 1959;32:285-310.
7. El mofty AM. Vitiligo and psoralens. Oxford: Pergamon Press;1968.
8. Ebbel B. The Papyrus Ebers. Copenhagen:Levin and Muntisgaard; 1937.
9. BB, Tawade YV, Dambre GM. Vitiligo(a monograph). Pune:Gokhale Mediservice Truust; 1989.
10. Nair BKH. Vitiligo – a retrospect. Int J Dermatol 1978; 17(9):755-7.

11. Kopera D.Historical aspects and definition of vitiligo. Clinics in dermatol 1997;15(6): 841-843.
12. Singh G, Ansari Z, Dwivedi RN. Vitiligo in ancient Indian medicine. Arch Dermatol 1974; 109:913.
13. Hu Z, Liu JB, Ma SS, Yang S, Zhang XJ. Profile of childhood vitiligo in China: An analysis of 541 patients . Pediatr Dermatol 2006; 23:114-6.
14. Handa S, Dogra S. Epidemiology of childhood vitiligo:A study of 625 patients from north India. Pediatr Dermatol 2003;20:207-10.
15. Pajvani U, Ahmad N, Wiley A, Levy RM, Kundu R, Mancini AJ et al.The relationship between family medical history and childhood vitiligo. J Am Acad Dermatol 2006;55:238-44.
16. Boiss RE Frontiersband controversies in pathology of vitiligo: separating the wheat from the chaff Exp Dermatol. 2009 July;18(7):583-585.
17. http://www.bio.davidson.edu/courses/Immunology/students/Spring 2013/leese/vitiligo.htm.
18. Dutta AK Vitiligo: Neural and Immunological linkages. Calcutta: Indira publications; 1988.
19. Wilson D. Etiology of Vitiligo. Lancet. 1971;ii:1298-1299.
20. Mazumdar PP, Das DK, Li CC. A genetical model for vitiligo. Am J Hum Genet. 1988;43:119.

21. Majumdar PP, Nordlund JJ, Nath SK. Pattern of familial aggregation of vitiligo. Arch Dermatol.1993;129:994.

22. Merlender J, Rywlin J. Heridity of acquired vitiligo(vitiligo in 3 generations.vActa Derm Venereol. 1940;21:583.

23. Ahnini T, Mcdonagh Aj, Wengraf DA, Lovewell TR, Vasilopoulos Y, Messenger AG, et al. The Autoimmune regulator gene is strongly associated with vitiligo. Br J Dermatol 2008; 159: 591-6.

24. Casp CB,She JX, McCormack WT. Genetic association of catalase gene(CAT) with vitiligo susceptibility. Pigment cell Res. 2002;15:62-66.

25. Jin Y, Mailloux CMGowan K, et al.NALP 1 in vitiligo associated multiple autoimmune disease. N Engl J Med. 2007;356:1256-25.

26. Mandry RC, Oritz IJ, Lugo Samo- Linos A, et al . Organ specific autoantibodies in vitiligo patients and relatives.Int J Dermatol. 1996;35:18-21.

27. Pawelek J, Lerner AB. 5-6 dihydroxyindole is a melanin precursor showing potent cytotoxicity. Nature. 1978; 276:627-628.

28. Schallreuter K, Pittelkow M. Defective calcium uptake in keratinocyte cell cultures from vitiliginous skin. Arch Dermatol Res. 988; 280:137-9.

29. Ramaih A, Puri N, Mojamdar M. Etiology of vitiligo. A new hypothesis. Acta Derm Venerol.1989;69:323-326.

30. Schallreuter, Wood JM, Pittelkow MR, et al. Regulation of melanin biosynthesis in human epidermis by tetrehydrobiopterin. Science. 1994;263:1444-6.
31. Ravinder Kumar, Davinder Prasad. Melanocytorrhagy and apoptosis in vitiligo: Connecting jigsaw pieces. Indian J Dermatol Venerol Leprol 2012;78:19-23.
32. Sarin KC, Kumar AS. A clinical study of vitiligo. Indian J of Dermatol Venerol Leprol. 1977; 43:311-314.
33. Ortonne JP, Mac Donald DM , Micoud A, et al. PUVA induced repigmentation of vitiligo, a histochemical and ultrstructural study. Br J Dermatol. 1979; 100:101-112.
34. Palit A, Inamadar AC. Childhood vitiligo. Indian J Dermatol Venereol Leprol 2012; 78:30-41.
35. Kanwar AJ, Dhar S, Kaur S. Vitiligo in children. Indian J Dermatol. 1993;38:47-52.
36. Ortonne J.P, Bahadoran P, Thomas B. Fitzpatrick, David B. Mosher and Yoshiaki Hori: Fitzpatrick's Textbook of Dermatology in General Medicine, sixth edition, chapter-90.
37. Hann SK, Lee HJ. Segmental vitiligo:clinical findings in 208 patients. J Am Acad Dermatol. 1996;35:671-674.
38. El Mofty AM,El Mofty M.Vitiligo, a symptom complex.Int J Dermatol.1998;19:237-244.

39. http:// www.cks. nhs.uk/ vitiligo/view_whole_topic.
40. Bhor U, Pande S. Scoring systems in dermatology. Indian J Dermatol Venereol Leprol 2006;72:315-21.
41. Sharma VK, Dawn G, Kumar B. Profile of Alopecia areata in northern India. Int J Dermatol.1996 Jan; 35(1):22-7.
42. Bor S, Feiwel M, Chanarin I. Vitiligo and its etiological relationship to organ specific autoimmune disease. Br J Dermatol.1969;91:83-88.
43. Reunala T, Collin P. Diseases associated with dermatitis herpetiformis. Br J Dermatol 1997; 156:135-8.
44. Von den Driesch P, Fartasch M, Hornstein OP. Chronic actinic dermatitis with vitiligo like pigmentation. Clin Exp Dermatol 1992 Jan; 17(1):38-43.
45. Peloro TM, Pride HB, Twenty nail dystrophy and vitiligo a rare association. J Am Acad Dermatol 1990; 40488-90.
46. Chan KF, Kong KH, Boey ML. Great Mimricry in a patient with tetraparesis: a case report. Arch Phys Med Rehabil 1995 Apr;76(4):391-3.
47. Jenkins RE, Kurwa AR, Atherton DJ, Blck MM. Neonatal lupus erythematosus. Clin Exp Dermatol 1994 Sep; 19(5):409-11.
48. Lerner AB, Nordlund JJ. Should vitiligo be induced in patients after resection of primary melanoma?Arch Dermatol. 1977;133:421.

49. Albert D, Nordlund J. Lerner A.Ocular abnormalities occurring with vitiligo. Opthalmology 1979;86:1145-58.

50. Harakati MS. Pernicious anemia in Arabs Blood cells Mol Dis. 1996; 22(2): 98-103.

51. Cho M, Cohen PR, Duvie M. Vitiligo and alopecia areata in patients with HIV infection.South Med J. 1995 Apr 88(4):489-91.

52. Moorthy RS, Inomata H, Rao NA.Vogt –Koyanagi- Harada syndrome. Surv Opthal 1995;39(4):265-92.

53. Dutta AK, Dutta PK. Pigmentary disorders in IADVL textbook and Atlas of Dermatology, Ed. RG Valia,First edition BI Publications 1994; Vol 1:518.

54. Carrie L Kovarik, Richard L Spielvogel, Gary R Kantor. Pigmentary disorders of skin. David Elder (ed).Levers Histopathology of the skin. 10th edition. New Delhi:Wolters Kluwer;2009.p 694-695.

55. Gokhale BB, Mehta LM. Histopathology of vitiliginous skin. Int. J. Dermatol 1983; 22:471-480.

56. Paller AS, Mancini AJ. Disorders of pigmentation. In:PallerAS, Mancini AJ, editors. Hurwitzclinical pediatric dermatology. 3 rd edition. Philadelphia: Elsevier Saunders;2006;265-305.

57. Sandipan Dhar, Pijush Dutta, Rajib Malakar. Pigmentary disorders.R.G Valia, Ameet R Valia. IADVL textbook of

dermatology.3rd edition.. Mumbai: Bhalani publishing house; 2008. p 749- 760.

58. Camacho F, Mazuecof J. Treatment of vitiligo with oral and topical phenylalanine; 6yrs of experience.Arch Dermatol.1999; 135:216-7.

59. Puri N, Van der Weel MB, de Wit FS, et al. Basic fibroblast growth factor promotes melanin synthesis by melanocytes. Arch Dermatol Res. 1996;288:633-5.

60. Punshi SK. Vitiligo and placental extract. Amaravathi :Maharashtra, India; 1989.

61. Pasricha JS, Khaitan BK. Oral mini- pulse therapy with betamethasone in vitiligo patients having extensive or fast spreading sisease. Int J Dermatol 1993;32:753-7.

62. Njod MD, Bos JD, Westerhof W. Treatment of generalised vitiligo in children with narrow-band UVB radiation therapy. J Am Acad Dermatol. 2000;42:245-53.

63. Tamesis ME, Morelli JG. Vitiligo treatment in childhood: A state of the art review.Pediatr Dermatol 2010;27:437-435.

64. Pathak MA et al: Safety and therapeutic effective of 8-methoxypsoralen, 4, 5, 8 trimethyl psoralen and psoralen in vitiligo photobiologic, toxicologic and and pharmacologic Aspects of Psoralens, Monograph 66, edited by MA Pathak Bethesda MD, National Cancer Institute, December 1984.

65. Gokhale BB, Tawade YV, Dambre GM. Vitiligo (a monograph). Pune:
Gokhale Mediservice Trust; 1989.
66. Adrain T, Orten B, Klemens R, et al. 5-Methoxypsoralen (Bergapten)
for photochemotherpy. J Am Arad Dermatol 1988;18:333-342.
67. Cormane RH, Siddiqui AH, Westerhof W,et al. Treatment of vitiligo with oral and topical phenylalanine; 6 years of experience. Arch Dermatol.1999;135:216-7.
68. Ortel B,Tanew A, Honigsman H. Treatment of vitiligo with Khellin and ultraviolet A.J Am Acad Dermatol. 1988;18:693-701.
69. Hadi S, Tinio P, Al – Ghaiti, Al – Qari H, Al – Helalat M, Lebowohl M. Treatment of vitiligo using the 308nm excimer laser. Photomer Laser Surg.2006; 24:354-7.

PROFORMA

Name Case no

Age Hospital no

Sex Date of enrolment

Address

Occupation

HISTORY:

Presenting complaints: No of patches, sites

Duration:

Activity:

Factors exacerbating –seasonal, infection, emotional, drugs, sunlight.

History of itching –

Hisory of drug intake prior to the onset of lesions.

History of injury – physical – present/absent.

Chemical – present/absent.

History of photosensitivity –

History of GIT disturbances -

Family history – Consanguinity in parents

Other family members with vitiligo

Associated diseases in family.

Associated autoimmune disease – hypothyroidism
pernicious anemia

Rheumatoid arthritis

addisons disease

Hyperthyroidism

Diabetes mellitus

Alopecia areata

Atopic dermatitis

Past history – Diabetes mellitus/ hypertension/ asthma/epilepsy/ tuberculosis.

Personal history – Diet/ apetite/ sleep/ bladder and bowel habits.

Examination

Sites – sunexposed/ covered areas.

Face, neck/ trunk/ genital/extremities.

Total Body surface involvement in percentage -

Leukotrichia – present/absent.

Koebners phenomenon – present/absent.

Type of vitiligo – focal / mucosal/acral/segmental.

Associated skin disease if any

Associated systemic disorder if any.

General Examination

1. Built
2. Height
3. Weight
4. Pallor
5. Icterus
6. Cyanosis
7. Clubbing
8. Lymphadenopathy
9. Edema
10. Vital – pulse, BP, RR
11. Systemic examination – CVS, RS, P/A, CNS.

INVESTIGATIONS

Hb
TC
DC
ESR
Peripheral smear
Blood group
Blood sugar
Blood urea
Serum creatinine
Liver Function Test
Thyroid Function Test

GROUP A – 0.03% TACROLIMUS ONLY.

	0w	2w	4w	6w	8w	10w	12w
Size of the patch							
No of patches							
Erythema							
Perifollicular repigmentation							
Pigmentation over margins							
Hair pigmentation							

	14w	16w	18w	20w	22w	24w
Size of the patch						
No of patches						
Erythema						
Perifollicular repigmentation						
Pigmentation over margins						
Hair pigmentation						

GROUP – B 0.03% TACROLIMUS AND TOPICAL STEROIDS.

	26w	28w	30w	32w	34w	36w	38w
Size of the patch							
No of patches							
Erythema							
Perifollicular repigmentation							
Pigmentation over margins							
Hair pigmentation							

	40w	42w	44w	46w	48w		
Size of the patch							
No of patches							
Erythema							
Perifollicular repigmentation							
Pigmentation over margins							
Hair pigmentation							

Physician global assessment

	0w	2w	4w	6w	8w	10w	12w
grade							

	14w	16w	18w	20w	22w	24w
grade						

	26w	28w	30w	32w	34w	36w
grade						

	38w	40w	42w	44w	46w	48w
grade						

Physician Global Assessment

Grade	Improvement in %	Comments
1	76%-100%	Excellent improvement
2	51%-75%	Marked improvement
3	26%-50%	Definite improvement
4	1% -25%	Minimal improvement
5	0%	No change

Patient global assessment score

	0w	2w	4w	6w	8w	10w	12w
Grade							

	14w	16w	18w	20w	22w	24w
Grade						

	26w	28w	30w	32w	34w	36w
Grade						

	38w	40w	42w	44w	46w	48w
Grade						

Grade

1 Much better

2 Slightly better

3 Same

4 Worse

Adverse events

Adverse Event	Severity	Onset	Course	Action	Relationship to study drug

KEY TO MASTER CHART

VASI –Vitiligo Area Scoring Index.

Phy G A - Physician Global Assessment score.

Pat G A – Patient Global Assessment score.

Group A: 0.03% Tacrolimus only.

Sl No	Name	Age	Sex	Duration of disease	Area involved	Type of vitiligo	VASI 0m	VASI 2m	VASI 4m	VASI 6m	VASI 8m	VASI 12m	Phy G A	Pat G A	Side effects
1	NANDA	5yrs	MALE	2yrs	GENITALIA	FOCAL	0.2	0.2	0.2	0.15	0.15	0.15	4	2	BURNING
2	NITHYA	13yrs	FEMALE	6months	TRUNK	FOCAL	0.05	0.025	0.025	0.005	0.005	0.005	1	2	-
3	RANJITH	12yrs	MALE	3yrs	FACE	FOCAL	0.1	0.09	0.09	0.075	0.05	0	1	2	-
4	DIVYA	8yrs	FEMALE	1yr	GENITALIA	FOCAL	0.375	0.375	0.375	0.375	0.225	0.225	3	2	BURNING
5	SATISH	14yrs	MALE	3yrs	TRUNK	SEGMENTAL	0.375	0.375	0.375	0.375	0.375	0.375	5	3	-
6	ELAIRASAN	9yrs	MALE	1yr	HAND	ACRAL	0.1	0.1	0.1	0.1	0.1	0.1	5	3	BURNING
7	SELVAM	8yrs	MALE	2yrs	GENITALIA	FOCAL	0.1	0.1	0.1	0.1	0.1	0.1	5	3	-
8	SAKTHI	11yrs	FEMALE	6months	GENITALIA	FOCAL	0.25	0.25	0.125	0.125	0.125	0.025	1	2	-
9	MADHU	10yrs	FEMALE	2yrs	TRUNK	FOCAL	0.375	0.375	0.375	0.375	0.375	0.375	5	3	-
10	VIDYA	7yrs	FEMALE	4yrs	TRUNK	FOCAL	0.375	0.375	0.375	0.375	0.225	0.225	3	2	-
11	SATYA	9yrs	FEMALE	3yrs	TRUNK	FOCAL	0.375	0.375	0.375	0.375	0.375	0.375	5	3	-
12	BALAN	11yrs	MALE	2yrs	FEET	ACRAL	0.1	0.1	0.1	0.1	0.1	0.1	5	3	BURNING
13	PRIYA	12yrs	FEMALE	1yr	FACE	FOCAL	0.05	0.025	0.025	0.005	0.005	0.005	1	1	-
14	GOPI	8yrs	MALE	4yrs	LOWERLIMB	FOCAL	0.375	0.375	0.375	0.375	0.375	0.375	5	3	-
15	NAGESH	5yrs	MALE	1yr	TRUNK	FOCAL	0.05	0.025	0.025	0.005	0.005	0.005	1	1	-
16	LATHA	6yrs	FEMALE	3yrs	GENITALIA	FOCAL	0.25	0.25	0.125	0.125	0.125	0.025	1	1	-
17	HEMALATHA	8yrs	FEMALE	4yrs	UPPERLIMB	FOCAL	0.06	0.06	0.06	0.06	0.06	0.06	5	3	-
18	RANJITHA	13yrs	FEMALE	3yrs	TRUNK	FOCAL	0.05	0.05	0.05	0.025	0.025	0.025	1	1	-
19	JAYAKUMAR	6yrs	MALE	2yrs	HAND	ACRAL	0.5	0.5	0.5	0.5	0.5	0.5	5	3	-
20	MAMTHA	7yrs	FEMALE	4yrs	GENITALIA	FOCAL	0.25	0.25	0.25	0.125	0.125	0.125	3	1	BURNING
21	MAHESH	11yrs	MALE	3yrs	FACE	FOCAL	0.05	0.025	0.025	0.005	0.005	0.005	1	1	-
22	RAJA	12yrs	MALE	4yrs	FACE	FOCAL	0.25	0.25	0.125	0.125	0.125	0.025	1	1	-
23	MURUGAN	8yrs	MALE	2yrs	FEET	ACRAL	0.06	0.06	0.06	0.06	0.06	0.06	5	3	-
24	RANI	9yrs	FEMALE	3yrs	FACE	FOCAL	0.05	0.025	0.025	0.005	0.005	0.005	1	1	-
25	ANAND		Dropout												

Group B: 0.03% Tacrolimus and topical corticosteroids.

Sl No	Name	Age	Sex	Duration of disease	Area involved	Type of vitiligo	VASI 0m	VASI 2m	VASI 4m	VASI 6m	VASI 8m	VASI 12m	Phy G A	Pat G A	Side effects
1	JAGAN	8yrs	MALE	2yrs	FACE	FOCAL	0.225	0.225	0.225	0.187	0.187	0.187	4	2	ATROPY
2	MANI	8yrs	MALE	3yrs	UPPERLIMB	FOCAL	0.75	0.75	0.5	0.5	0.5	0.5	3	1	-
3	PAVITHRA	10yrs	FEMALE	4yrs	FACE	SEGMENTAL	0.05	0.025	0.025	0.005	0.005	0.005	1	2	ATROPY
4	RAJ	13yrs	MALE	5yrs	UPPERLIMB	FOCAL	1	0.9	0.75	0.5	0.5	0.5	3	1	-
5	RAKESH	10yrs	MALE	2yrs	UPPERLIMB	FOCAL	1.5	1.5	1	1	1	1	3	1	-
6	LAKSHMI	7yrs	FEMALE	1yr	TRUNK	FOCAL	3.6	3.6	3	3	3	3	4	2	-
7	SARANYA	6yrs	FEMALE	2yrs	LOWERLIMB	FOCAL	0.25	0.25	0.25	0.1	0.1	0	1	1	-
8	ANIL	10yrs	MALE	3yrs	FEET	ACRAL	0.06	0.06	0.06	0.06	0.06	0.06	5	3	-
9	BALAJI	5yrs	MALE	4yrs	FEET	ACRAL	0.375	0.375	0.375	0.375	0.375	0.375	5	3	-
10	ASHWIN	11yrs	MALE	1yr	HAND	ACRAL	1.35	1.35	1.35	1.35	1.35	1.35	5	3	-
11	HARISH	12yrs	MALE	4yrs	LOWERLIMB	FOCAL	0.375	0.375	0.375	0.25	0.25	0.25	3	2	-
12	PAVITHRA	10yrs	FEMALE	3yrs	FEET	ACRAL	0.06	0.06	0.06	0.06	0.06	0.06	5	3	-
13	KAVIBHARATHI	7yrs	FEMALE	2yrs	LOWERLIMB	FOCAL	0.1	0.1	0.1	0	0	0	1	1	-
14	SUMATHI	7yrs	FEMALE	2yrs	TRUNK	FOCAL	0.75	0.75	0.75	0.5	0.5	0.5	3	2	-
15	JAYAKUMAR	10yrs	MALE	3yrs	TRUNK	FOCAL	0.5	0.5	0.5	0.5	0.5	0.5	5	3	-
16	ASHA	10yrs	FEMALE	2yrs	FACE	FOCAL	1	1	0.75	0.5	0.25	0.25	2	1	-
17	PINKY	10yrs	FEMALE	2yrs	TRUNK	FOCAL	1	1	0.75	0.5	0.25	0.25	2	1	-
18	BHARATHI	8yrs	FEMALE	1yr	GENITALIA	FOCAL	0.1	0.1	0.1	0	0	0	1	1	-
19	AKSHAYA	10yrs	FEMALE	3yrs	GENITALIA	FOCAL	0.1	0.09	0.09	0.075	0.05	0.05	3	2	-
20	PADMAPRIYA	8yrs	FEMALE	1yr	UPPERLIMB	FOCAL	0.1	0.09	0.09	0.075	0.05	0.05	3	2	-
21	BHARATH	10yrs	MALE	2.6yrs	LOWERLIMB	FOCAL	0.75	0.75	0.5	0.5	0.5	0.5	3	2	-
22	SHAKTHIVEL	9yrs	MALE	3yrs	FEET	ACRAL	0.1	0.1	0.1	0.1	0.1	0.1	5	3	-
23	MURUGAN	7yrs	MALE	6months	HAND	ACRAL	0.06	0.06	0.06	0.06	0.06	0.06	5	3	-
24	SARANYA			Dropout											
25	RAMKUMAR			Dropout											